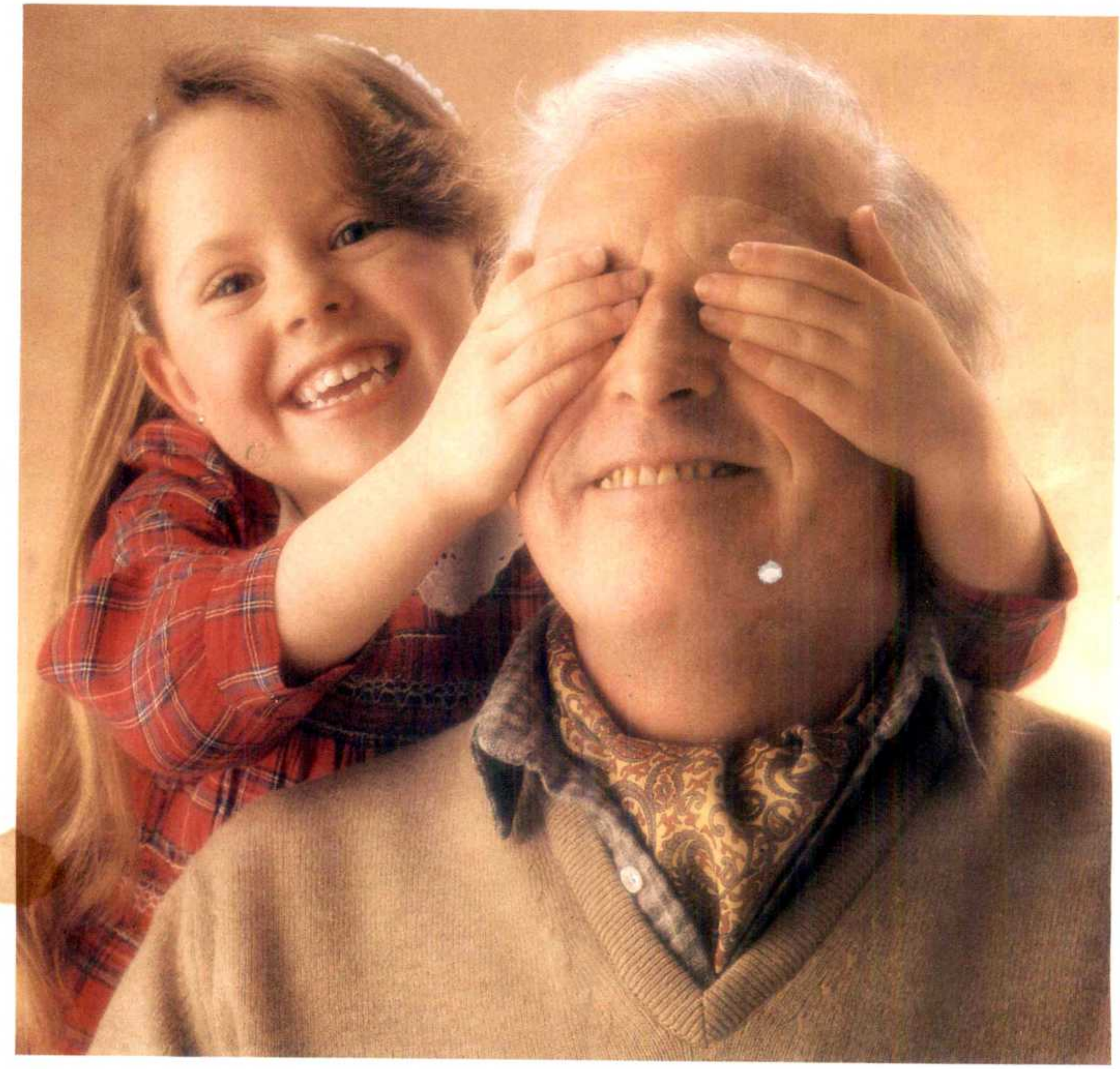
Guess which prostate cancer treatment most patients would choose.



In a recent study[1], 57 prostate cancer patients were invited to participate in choosing their treatment. All were informed that the two treatments available, sub-capsular orchidectomy or 'Zoladex', were similar in efficacy and side effects. 49 of the patients (86%) opted for 'Zoladex'.

A recent trial[2] has established the equivalence of 'Zoladex' to orchidectomy.

Zoladex
goserelin

Effective therapy without surgery.

'ZOLADEX' PRESCRIBING NOTES.
Consult data sheet before prescribing. Use: Prostate cancer suitable for hormonal manipulation. **Presentation:** A sterile depot containing goserelin 3.6mg. **Dosage and administration:** One depot injected subcutaneously into the anterior abdominal wall every 28 days. **Precautions:** Patients at particular risk of developing ureteric obstruction or spinal cord compression. Consider initial use of an anti-androgen at the start of therapy. An increase in benign pituitary tumours has been observed in male rats following long-term repeated dosing. This finding is similar to that previously noted in this species following surgical castration (relevance to man not established). **Side effects:** Hot flushes, decrease in libido and occasional breast swelling and tenderness. Skin rashes (generally mild). Occasional mild bruising at injection site. Initial transient increase in serum testosterone may cause temporary increase in bone pain. **Product licence number:** 29/0198. **Basic NHS cost:** £114 per depot. 'Zoladex' is a trademark.
Further information is available from: ICI Pharmaceuticals (UK), Southbank, Alderley Park, Macclesfield, Cheshire. SK10 4TF.
Reference 1. Lunglmayr G, Girsch E. In Chisholm G D ed. *'Zoladex' – a new treatment for prostatic cancer. International Congress and Symposium Series.* 125. London: RSM Series, 1987: 47-51.
2. Peeling W B. Proceedings of the 'Zoladex' Scientific Launch Meeting 1987.

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23

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Cover picture

This month the cover of The British Journal of Surgery bears the flag of the European Community. Our style in recent years has been to carry the emblems of surgical colleges and societies from around the world to emphasize our commitment to surgery world-wide. This month we modify this tradition for two reasons.

First, in October the inaugural Eurochirurgie meeting (incorporating all the surgical academies, colleges and societies in Europe and Scandinavia) will be held in Paris. This first 'Congrès Européen de Chirurgie' marks an important new venture for European surgeons. The Eurochirurgie Congress is to be an annual event held in Brussels in 1992, in London in 1993 and in Berlin in 1994.

Our second reason for carrying the European Community flag is to emphasize our commitment to European surgery. Nowadays, The British Journal of Surgery is published in three editions: the main English language edition for world-wide circulation, the Spanish edition published in the Spanish language in Spain and circulating in Spain and South America, and an Indian edition published in Bombay. The three editions carry the same articles, are in the same format and are managed by the same editorial board; they are an attempt to reach out to surgeons world-wide. Today, 60 per cent of material published in The British Journal of Surgery is from UK sources and over 20 per cent is from the rest of Western Europe.

Our circulation reflects this image – 50 per cent of our main English language edition is mailed to Western European addresses and, of course, most of the Spanish edition ends up in Spain. Thus, we are already a European surgical journal.

To date, European harmonization and integration has not had many easy successes, but the Euroflag is definitely one of these achievements which should appeal to the committed Europhile. It is the symbol of an embryonic 'nationalism' developing within the member states. However, its provenance is uncertain if not completely obscure. Most definitely it was not the work of some intergovernmental compromise. The Council just adopted it and then the Commission appropriated it in the absence of anything else European. The 12 stars do not represent the member states, there have always been 12 stars on the Euroflag even when there were only six contracting parties.

For a flag signifying so much that is anathema to so many it has led a relatively boring life. It has not been burned, mangled or defaced and, although it is possible to hang it upside down, it is not recorded whether this has happened as yet. Extensive research indicates that even verbose politicians have had nothing whatsoever noteworthy to say about the design of the Euroflag... so far!

Brendan M. W. Devlin

The British Journal of Surgery

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Volume 77 Number 9 September 1990

LEADING ARTICLES

Limitations of tumour markers in screening 961
J. E. Roulston

Endoscopic sclerotherapy: the far and near effects 963
A. Chaudhary, M. Tatke and R. C. Aranya

REVIEWS

Surgical aspects of malaria 964
E. J. Gibney

Pylorus preserving pancreatoduodenectomy: an overview 968
P. A. Grace, H. A. Pitt and W. P. Longmire

Operative choledochoscopy: common bile duct exploration is incomplete without it 975
R. W. Motson and L. A. Wetter

Primary hepatic malignancy: the role of liver transplantation 983
T. Ismail, L. Angrisani, B. K. Gunson, S. G. Hübscher, J. A. C. Buckels, J. M. Neuberger, E. Elias and P. McMaster

Management of intrahepatic calculi in Caroli's disease by extracorporeal shock wave lithotripsy (case report) 987
P. H. Lointier, Ph. Kauffmann, Ph. Francannet, D. Pezet and J. Chipponi

Mucosal intussusception to avoid ascending cholangitis 989
T. J.-Yeh, T.-W. Chin, W.-C. Tsai and C.-F. Wei

Differing effects of pethidine and morphine on sphincter of Oddi motility 992
A. Thune, R. A. Baker, G. T. P. Saccone, H. Owen and J. Toouli

Plasma cell granuloma of the distal oesophagus (case report) 996
J. L. Seco, M. Claver, M. Bengoechea, G. Moral and J. L. Santamaria

Intraoperative ultrasonography and the detection of liver metastases in patients with colorectal cancer 998
A. K. Olsen

Papillary cystic neoplasm of the pancreas: radiological and pathological characteristics in 11 cases 1000
K. Yamaguchi, R. Hirakata and K. Kitamura

Choice of emergency operative procedure for bleeding duodenal ulcer 1004
P. S. Hunt and R. L. E. McIntyre

Laparoscopic treatment of perforated peptic ulcer (short note) 1006
P. Mouret, Y. François, J. Vignal, X. Barth and R. Lombard-Platet

Anterior lesser curve seromyotomy and posterior truncal vagotomy *versus* truncal vagotomy and pyloroplasty in the treatment of chronic duodenal ulcer 1007
T. V. Taylor, J. P. Lythgoe, J. B. McFarland, I. T. Gilmore, P. E. Thomas and G. H. Ferguson

CA72-4: a new tumour marker for gastric cancer 1010
D. J. Byrne, M. C. K. Browning and A. Cuschieri

Primary gastric carcinoids: a view on management (short note) 1013
M. G. Davies, G. O'Dowd, G. P. McEntee and T. P. J. Hennessey

Failure of nutritional recovery after total gastrectomy 1015
F. T. Curran and G. L. Hill

Feeding regimens after pyloromyotomy 1018
R. A. Wheeler, A. S. Najmaldin, N. Stoodley, D. M. Griffiths, D. M. Burge and J. D. Atwell

Treatment of adenocarcinoma of the cardia with synchronous chemotherapy and radiotherapy 1020
P. G. Gill, G. G. Jamieson, J. Denham, P. G. Devitt, A. Ahmad, E. Yeoh and A. M. Jones

Gastric outlet obstruction now predicts malignancy (short note) 1023
C. D. Johnson and H. Ellis

Manometric evaluation of jejunal limb after total gastrectomy and Roux–Orr anastomosis for gastric cancer 1025
G. Bassotti, P. Gullà, C. Betti, W. E. Whitehead and A. Morelli

Glyceryl trinitrate in the management of a biliary fistula (case report) 1029
D. Sharma, G. T. Sunderland and I. F. Kerr

Single lumen ileum with myectomy: a possible alternative to the pelvic reservoir in restorative proctocolectomy 1030
P. M. Sagar, P. J. Holdsworth, R. F. G. J. King, G. Salter and D. Johnston

Elective resection for diverticular disease of the sigmoid colon 1036
J. Moreaux and C. Vons

Gracilis muscle transposition for faecal incontinence 1039
J. Christiansen, M. Sørensen and O. Ø. Rasmussen

Survey of the use of thrombolysis for acute limb ischaemia in the UK and Ireland 1041
J. J. Earnshaw and J. F. L. Shaw

Resympathectomy of the upper extremity 1043
E. J. H. van Rhede van der Kloot and P. J. G. Jörning

Endoscopic transthoracic electrocautery of the sympathetic chain for palmar and axillary hyperhidrosis 1046
J. Byrne, T. N. Walsh and W. P. Hederman

Transcutaneous oxygen tensions in assessing the treatment of healed venous ulcers 1050
M. C. Stacey, K. G. Burnand, G. T. Layer and M. Pattison

Venous stasis and vein lumen changes during surgery 1055
P. D. Coleridge-Smith, J. H. Hasty and J. H. Scurr

Use of skin graft knife in the treatment of giant perianal condyloma acuminatum (surgical workshop) 1060
M. J. Notaras, W. J. G. Murray and S. Manek

Percutaneous gastrostomy: an alternative endoscopic approach (surgical workshop) 1062
S. Y. Iftikhar and A. S. McIntyre

FOR DEBATE

Cancer of the colon and rectum 1063
Seventh King's Fund Forum: Consensus statement

SURGERY PAPER

Human Kupffer cells are cytotoxic against human colon adenocarcinoma 1066
M. S. Roh, L. Wang, C. Oyedeji, M. E. LeRoux, S. A. Curley, R. E. Pollock and J. Klostergaard

BOOK REVIEWS AND CORRESPONDENCE 1071

NOTICES AND ANNOUNCEMENTS 1078

SURGERY AND THE AMERICAN JOURNAL OF SURGERY CONTENTS 1079

The British Journal of Surgery

Published by Butterworth-Heinemann for the British Journal of Surgery Society Limited
The Journal is specially related with The Association of Surgeons of Great Britain and Ireland and The Surgical Research Society

Volume 77 Number 10 October 1990

LEADING ARTICLES

Infection and the burn patient **1081**
B. A. Pruitt Jr.

Thrombolytic therapy in peripheral vascular disease **1083**
H. Hess

ASSOCIATION OF SURGEONS OF GREAT BRITAIN AND IRELAND

Bile acids and the increased risk of colorectal tumours after truncal vagotomy **1085**
F. J. Mullan, H. K. Wilson, C. W. Majury, J. O. M. Mills, A. J. Cromie, G. R. Campbell and S. T. D. McKelvey

Urinary tissue factor activity in colorectal disease **1091**
N. Carty, I. Taylor, O. S. Roath, K. El-Baruni and J. L. Francis

Intraoperative air testing of colorectal anastomoses: a prospective, randomized trial **1095**
J. D. Beard, M. L. Nicholson, R. D. Sayers, D. Lloyd and N. W. Everson

Malignant left-sided large bowel obstruction managed by subtotal/total colectomy **1098**
B. M. Stephenson, A. A. Shandall, R. Farouk and G. Griffith

Complications of diverticular disease and non-steroidal anti-inflammatory drugs: a prospective study **1103**
R. G. Wilson, A. N. Smith and I. M. C. Macintyre

Intraoperative testing of colorectal anastomosis can be misleading (short note) **1105**
G. A. Pritchard, F. F. Krouma and J. Stamatakis

Blood transfusion and recurrence of colorectal cancer: the role of platelet derived growth factors **1106**
R. J. Lawrance, A. J. Cooper, M. Loizidou, P. Alexander and I. Taylor

Mastalgia refractory to drug treatment **1110**
C. A. Gateley, P. R. Maddox, R. E. Mansel and L. E. Hughes

Experimental study of starch-induced intraperitoneal adhesions **1113**
G. P. McEntee, R. C. Stuart, P. J. Byrne, E. Leen and T. P. Hennessy

Pulse oximetry: a new non-invasive assessment of peripheral arterial occlusive disease **1115**
W. P. Joyce, K. Walsh, D. B. Gough, T. F. Gorey and J. M. Fitzpatrick

Through-knee amputation in high-risk patients with vascular disease: indications, complications and rehabilitation **1118**
B. J. Moran, P. Buttenshaw, M. Mulcahy and K. P. Robinson

Effect of surgery on the systemic inflammatory response to intermittent claudication **1121**
N. C. Hickey, P. Gosling, S. Baar, C. P. Shearman and M. H. Simms

Graft stenosis: justification for 1-year surveillance **1125**
P. R. Taylor, J. H. N. Wolfe, M. R. Tyrrell, A. O. Mansfield, A. N. Nicolaides and R. E. Houston

Recent changes in the treatment of aortoiliac occlusive disease by the Oxford Regional Vascular Service **1129**
A. H. Davies, P. Ramarakha, J. Collin and P. J. Morris

Conservative management of asymptomatic popliteal aneurysm **1132**
R. C. Bowyer, S. J. Cawthorn, W. J. Walker and A. E. B. Giddings

Acute limb ischaemia: the place of intravenous streptokinase **1136**
J. J. Earnshaw, C. Cosgrove, D. C. Wilkins and B. P. Bliss

Dynamic angioplasty of total arterial occlusions (short note) **1139**
A. A. Gehani, K. Sheard, S. Ashley, S. Brooks, R. C. Kester and M. R. Rees

Trauma centres and the efficient use of financial resources **1142**
T. J. O'Kelly and S. Westaby

On-table pancreatography: importance in planning operative strategy **1145**
L. A. Desa and R. C. N. Williamson

Laser recanalization *versus* endoscopic intubation in the palliation of malignant dysphagia 1151
D. Alderson and P. D. Wright

Stress in surgeons 1154
A. Green, H. L. Duthie, H. L. Young and T. J. Peters

REVIEWS

Aetiology of pancreatic cancer 1159
G. Haddock and D. C. Carter

Abdominal wall pain: an alternative diagnosis 1167
N. C. Gallegos and M. Hobsley

Parathyroid autotransplantation 1171
A. Senapati and A. E. Young

Surgery in patients on long-term steroid therapy. a tentative model for risk assessment 1175
R. Reding, L. A. Michel, J. Donckier, L. de Canniere and J. Jamart

Premorphological metabolic changes in human breast carcinogenesis 1179
E. W. M. McDermott, E. T. Barron, P. P. A. Smyth and N. J. O'Higgins

Selection of patients with internal intussusception of the rectum for posterior rectopexy (short note) 1183
R. H. Kruyt, J. B. V. M. Delemarre, H. G. Gooszen and H. J. Vogel

Colostomy irrigation: a clinical and scintigraphic comparison between three different irrigation volumes (short note) 1185
H. H. Meyhoff, B. Andersen and S. Levin Nielsen

Treatment for paraphimosis: the puncture technique (surgical workshop) 1186
F. C. Hamdy and K. J. Hastie

Treatment of trans-sphincteric fistulae by full thickness anorectal advancement flaps (surgical workshop) 1187
P. Lewis and D. C. C. Bartolo

Cholecystectomy through a 5 cm subcostal incision (short note) 1189
P. J. O'Dwyer, J. J. Murphy and N. J. O'Higgins

Localization of impalpable breast lesions: a new device (surgical workshop) 1191
M. A. Chaudary, J. F. Reidy, R. Chaudhuri, R. R. Millis, J. L. Hayward and I. S. Fentiman

CORRESPONDENCE 1193

BOOK REVIEWS 1196

NOTICES AND ANNOUNCEMENTS 1198

SURGERY AND THE AMERICAN JOURNAL OF SURGERY CONTENTS 1199

Cover picture

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The cover shows the Presidential badge of the Association

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Volume 77 Number 11 November 1990

LEADING ARTICLES

Extrahepatic portal vein obstruction 1201
P. Sahni, G. K. Pande and S. Nundy

General surgical problems in pregnancy 1203
J. Smoleniec and D. James

REVIEW

Pancreatic ischaemia in experimental acute pancreatitis: mechanism, significance and therapy 1205
E. Klar, K. Messmer, A. L. Warshaw and C. Herfarth

Preoperative cytology and mammography in patients with single-duct nipple discharge treated by surgery 1211
A. Fung, Z. Rayter, C. Fisher, D. M. King and P. Trott

Microdochectomy for discharge from a single lactiferous duct 1213
M. Welch, D. Durrans, J. Gonzalez, H. Daya and A. M. W. C. Owen

Fine needle aspiration biopsy in the diagnosis and management of fibroadenoma of the breast 1215
T. K. Walters, J. Zuckerman, A. Nisbet-Smith, E. Hudson, Y. Chia and M. Burke

Microdochectomy: the precise identification of the suspicious duct (surgical workshop) 1217
J. D. Berná, M. Madrigal, J. Guirao, I. Arcas and S. Gómez

Meakin adjuvant regimen in premenopausal patients with breast cancer 1219
D. Smith, J. A. Dewar, J. M. Horobin, J. S. Scott and P. E. Preece

Reduced psychological morbidity after breast conservation 1221
J. M. McArdle, A. V. M. Hughson and C. S. McArdle

Impaired polymorphonuclear leucocyte function in patients undergoing hepatectomy: adenylate energy charge and superoxide anion production in relation to hepatic mitochondrial redox state 1224
H. Higashiyama, H. Egawa, S. Iwata, Y. Wada, Y. Shimahara, M. Sasada, K. Mori and K. Ozawa

Development and reversibility of T lymphocyte dysfunction in experimental obstructive jaundice 1229
R. L. E. Thompson, M. Hoper, T. Diamond and B. J. Rowlands

Assessment of the biliary tract after liver transplantation: T tube cholangiography or IODIDA scanning 1233
M. Anselmi, S. Lancberg, M. Deakin, E. Lanchbury, Z. Drolc, F. Burrows, E. Elias and P. McMaster

Regional chemotherapy for colorectal liver metastases: a phase II evaluation of targeted hepatic arterial 5-fluorouracil for colorectal liver metastases 1238
J. A. Goldberg, D. J. Kerr, N. Wilmott, J. H. McKillop and C. S. McArdle

Hepatic metastases from colorectal carcinoma: impact of surgical resection on the natural history 1241
J. Scheele, R. Stangl and A. Altendorf-Hofmann

Extended hepatectomy for hepatocellular carcinoma 1247
S. Al-Hadeedi, T. K. Choi and J. Wong

Antigen CA 19-9 and mucinous cystadenoma of the pancreas (case report) 1250
F. Pâris, A. Kerschen and D. Jaeck

Effective intraperitoneal antiprotease therapy for taurocholate-induced pancreatitis in rats 1252
C. Wilson and C. W. Imrie

Free radical inhibition and serial chemiluminescence in evolving experimental pancreatitis 1256
D. B. Gough, B. Boyle, W. P. Joyce, C. P. Delaney, K. F. McGeeney, T. F. Gorey and J. M. Fitzpatrick

Prediction of outcome in acute pancreatitis: a comparative study of APACHE II, clinical assessment and multiple factor scoring systems 1260
C. Wilson, D. I. Heath and C. W. Imrie

Gallstone clearance: a randomized study of extracorporeal shock wave lithotripsy and chemical dissolution 1265
A. Darzi, A. Leahy, C. O'Morain, W. A. Tanner and F. B. V. Keane

Gallbladder surgery following cholecystlithotripsy: suggested guidelines for treatment **1268**
S. H. Lee and H. J. Burhenne

Treatment of sleep apnoea by vertical gastroplasty (case report) **1271**
C. L. Summers, J. R. Stradling and R. M. Baddeley

Surgical presentation of Kawasaki disease (mucocutaneous lymph node syndrome) **1273**
R. A. Wheeler, A. S. Najmaldin, M. Soubra, D. M Griffiths, D. M. Burge and J. D. Atwell

Vastus lateralis myocutaneous flap for reconstruction of defects around the groin and pelvis **1275**
N. Waterhouse and C. Healy

Massive gastrointestinal haemorrhage due to ileal varices (case report) **1277**
P. Lewis, B. F. Warren and D. C. C. Bartolo

Association between extent of colonic mucosal sialomucin change and subsequent local recurrence after curative excision of primary colorectal cancer **1279**
P M. Dawson, N. A. Habib, S. Fane, H. C. Rees, C. B. Wood and T. G. Allen-Mersh

Pouchitis following colectomy and ileal reservoir construction for familial adenomatous polyposis (case report) **1283**
W. A. Kmiot, M. R. Williams and M. R. B Keighley

Direct measurement of collagenase in colonic anastomosis **1284**
N. L. Chowcat, F. J. Savage, M. R. Lewin and P. B. Boulos

Intraluminal pressure adjacent to left colonic anastomoses **1288**
D. S. Burkitt and I A Donovan

Irreducible inguinal hernia in children below two years of age **1291**
N. Davies, A. Najmaldin and D. M Burge

Effect of hydrocele on testis and spermatogenesis **1293**
M. C. Dandapat, N. C. Padhi and A. P. Patra

New isotopic technique for detecting prosthetic arterial graft infection: ^{99m}Tc-hexametazime-labelled leucocyte imaging **1295**
R L. Insall, N. A. G. Jones, J. Chamberlain, D. Lambert and P. M. Keavey

Buerger's colour **1299**
T. Kimura, S. Yoshizaki, N. Tsushima, M. Sano and G. Hanai

Thallous chloride uptake and DNA profile in parathyroid adenomas **1302**
G. L. Carlson, J. R. Farndon, B. K. Shenton, C. B. Clayton and I. D. A Johnston

Duodenogastric reflux and gastric histology after cholecystectomy with or without sphincteroplasty **1305**
D. Lorusso, F. Pezzolla, C. Montesani, P Giorgio, M. L Caruso, A. Cavallini, V. Guerra and G. Misciagna

BRITISH ASSOCIATION OF ENDOCRINE SURGEONS: ABSTRACTS **A1308**

CORRESPONDENCE **1313**

BOOK REVIEWS **1316**

NOTICES AND ANNOUNCEMENTS **1318**

SURGERY AND THE AMERICAN JOURNAL OF SURGERY CONTENTS **1319**

Cover picture

Lord Lister Coat of Arms

The original painting of the Arms shown on the cover of the Journal was prepared under the direction of York Herald of Arms (Conrad Swan CVO, PhD, FSA)

Br. J. Surg. 1990, Vol. 77, September, 961–962

Limitations of tumour markers in screening

The role of tumour markers in monitoring patients with certain types of cancer is fairly well established. However, their usefulness in screening for earlier diagnosis has severe limitations[1]. There are many examples in the literature of apparently promising novel markers which, on subsequent closer scrutiny, fail to fulfil expectations[2].

One possible reason for this is that, in pilot studies, the researchers may use hospital inpatients with advanced bulky disease as the test group. Significant positivity in such a group cannot be extrapolated to patients with early-stage disease, for whose benefit marker screens are largely intended; therefore subsequent studies conducted on a more appropriate patient group may yield less impressive results.

A second possible cause may relate to the setting of the cut-off value (used to define a positive result). It is commonplace to set this value empirically on the basis of the marker cut-off value which misclassifies (either as false negative or false positive) the least number of patients. What one cannot then do, however, is apply statistical tests such as a χ^2 test to the same group of data. Using the same data both to establish a cut-off and to assess a test's predictive capabilities inevitably leads to an over-optimistic P value which will prove unattainable in subsequent studies using independent data[3].

A third reason relates to the prevalence of the disease in the group under study. A test which is of genuine clinical value in the specialist clinic may be useless or genuinely misleading to the general practitioner because the disease prevalence is too low in the latter situation. Thus, a tumour marker which is of value in monitoring recurrence or relapse may be devoid of use in screening.

How do we assess a putative test? It is customary to describe tests in terms of their sensitivity and their specificity. The sensitivity of a test is a measure of its ability to show a positive result in patients with the disease and is calculated as (true positive/(true positive+false negative)). Conversely, the specificity is a measure of the test's capacity to show negative results in the absence of disease; this is calculated as (true negative/(true negative+false positive)). Sensitivity, therefore, is calculated solely on patients with disease and specificity solely on those without disease; hence, as both are independent of prevalence the clinical usefulness of a test cannot be assessed by these two parameters alone. It is also important to note that one cannot optimize both sensitivity and specificity. If one raises the value of the cut-off one will generate fewer false positives and increase specificity. By the same action however one will increase the likelihood of missing more true positives and thereby sensitivity will be reduced.

This begs the question, which is more important in a screening context, sensitivity or specificity? If we assume that a false positive and a false negative result are equally dangerous in the clinical context, we can therefore define an index of misclassification, Z = number of false negatives + number of false positives. The number of false negatives can be calculated as the inability of the test to pick up the disease, that is (1-sensitivity), multiplied by the disease prevalence, X. Similarly the number of false positives can be calculated from the inability of the test to detect true negatives (1-specificity) multiplied by the prevalence of non-disease in the group, (1-X).

Therefore, $Z = (1\text{-sensitivity})X + (1\text{-specificity})\ (1-X)$.

In screening the prevalence of disease is very low. We can see from the above equation that as prevalence, X, nears zero then the index of misclassification, Z, will be described as $Z = (1 - \text{specificity})$. Therefore to minimize Z we should maximize specificity rather than sensitivity. Indeed, specificity is the first parameter calculated in a pilot screen as false negatives are not readily apparent; a true assessment of sensitivity may take years depending on the prevalence of the disease in the test population. To establish clinical usefulness, therefore, we need to consider a measure which takes account of the disease prevalence.

Probably the single most useful test characteristic to the clinician is the positive predictive value. This is defined as the proportion, usually the percentage, of the

0007–1323/90/090961–02

Table 1 *The effect of prevalence on predictive value*

Prevalence of disease (%)	Positive predictive value (95 per cent sensitivity + specificity)	Positive predictive value (99 per cent sensitivity + specificity)
0·02	0	2·0
0·1	1·9	9·0
1	16·1	50·0
2	27·9	66·9
5	50·0	83·9
50	95·0	99·0

positive tests which are true positive. It is therefore defined as (true positive/(true positive + false positive)) and this gives a direct indication of the 'odds', i.e. what is the probability that this elevated marker result is due to the disease in question? Changing the disease prevalence dramatically alters the positive predictive value for a test (see *Table 1*). It is vital therefore to consider the context in which a putative marker is to be used.

Undoubtedly the most successful tumour marker used in screening is that of human chorionic gonadotrophin (HCG) in choriocarcinoma. This tumour develops in 5–10 per cent of women who have had a hydatidiform mole. The assays in current use have excellent clinical and analytical specificity and sensitivity, a measurable spike of HCG being produced by as few as 10^5 cells. HCG is also measurable in urine which facilitates follow-up and increases patient compliance. Screening with HCG, together with the high chemosensitivity of the tumour, has drastically reduced mortality over the last 20 years. However, it is worth noting that the single factor which makes screening effective is the high prevalence of the disease in the group being screened.

The positive predictive value of HCG, assuming a 10 per cent prevalence and a 99 per cent sensitivity and specificity for the test is of the order of 92 per cent. If, however, no such high-risk subgroup were identified and it was necessary to screen all women who had undergone full-term pregnancy, the prevalence of choriocarcinoma in this context is 1/40 000 and the positive predictive value of the test would be virtually zero.

In a screening exercise in ovarian cancer, post-menopausal women were screened using the serum marker CA-125. When first reported[4], 1010 women had been tested and 31 found to have elevated levels. These 31 women then underwent ultrasound examination; three were deemed to have an abnormality and underwent surgery. One had early ovarian cancer. CA-125 alone, in this study, therefore, has a positive predictive value of 1/31 or 3 per cent, despite a sensitivity of 100 per cent (1/1) and a specificity of 97 per cent (978/1009)! It is not necessary to undertake large and expensive screening programmes to determine a test's predictive value; this is calculable from a knowledge of the test sensitivity and specificity and the disease prevalence. As the late Sir Peter Medawar once said, 'Since Isaac Newton we no longer have to chart the fall of each apple'.

In conclusion, while the serological markers available to us can provide very useful information when used sensibly they are unlikely to assist in earlier diagnosis or in screening exercises. Unless tests where sensitivity and specificity are 100 per cent can be offered, the low prevalence of the diseases will inevitably reduce the positive predictive value to a very low level. We perhaps should be placing greater research resources in trying to identify potential high risk groups, either by epidemiological or genetic research, which could then be usefully and efficiently monitored by serological and other tests.

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Br. J. Surg. 1990, Vol. 77, September, 963

Endoscopic sclerotherapy: the far and near effects

The last few years have seen a revival of interest in endoscopic sclerotherapy for bleeding oesophageal varices. Sclerotherapy has not only been widely used in the management of acute variceal bleeding, but also has been recommended on a prophylactic basis for a selected group of patients. With widespread use of endoscopic sclerotherapy, emergency portosystemic shunting has gone into disfavour in most centres, the proponents of sclerotherapy claiming equally good results in terms of arrest of bleeding with much smaller mortality and morbidity rates. Although acutely bleeding varices can be controlled by standard medical treatment including emergency sclerotherapy in 50–80 per cent of cases[1,2], rebleeding occurs in 17–33 per cent patients and varices have been seen to recur in some two-thirds of patients[3–5]. Most studies of sclerotherapy have focused only on its local complications such as oesophageal ulceration, perforation, and oesophageal strictures. Systemic dissemination of the injected sclerosant has been detected and distant complications like brain abscess and digital gangrene have been reported following endoscopic sclerotherapy[6,7]. A recent report by Hunter *et al.*[8] has shown a new disturbing complication of the effect of dissemination of the sclerosant into the venous system. Definite histological changes of intimal thickening, medial fibrosis and destruction of venous architecture have been seen in the portal veins in patients receiving sclerotherapy and then undergoing portacaval shunts. These changes might be responsible for subsequent shunt occlusion in such patients. We also are studying splenic vein histology in patients undergoing splenorenal shunt following sclerotherapy and have found generalized changes in the walls of the veins ranging from increased fibrosis to intimal and medial destruction and microthrombi. In addition, it is our observation that, in patients receiving long term sclerotherapy and later coming to shunt surgery, the splenic vein is more densely adherent to the pancreas due to extensive periadventitial fibrosis. Thus, surgery in these patients is more difficult and time consuming. These observations lead us to question whether endoscopic sclerotherapy is as innocuous as is generally believed. Though the local complications are soon obvious, complication due to systemic dissemination of sclerosant may be masked. Are these preliminary observations a valid argument for advocating a more selective and restricted use of sclerotherapy in patients who are potential candidates for a portosystemic shunt or a liver transplant? This aspect of sclerotherapy needs more evaluation.

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Surgical aspects of malaria

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The spread of drug-resistant organisms and increased international travel makes malaria a disorder of ever-increasing importance. This report reviews those aspects of malaria of surgical relevance. The importance of the spleen in host defence against malaria and other infections makes splenic preservation desirable whenever possible after rupture of the spleen. Tropical splenomegaly is caused by an abnormal immune response to malaria and is best managed medically. Careful selection of blood donors is essential to prevent transfusion malaria, and routine antimalarial prophylaxis is indicated for blood recipients in many endemic areas. The risk of postoperative malaria may justify chemoprophylaxis in certain patients.

Keywords: Malaria, surgery, tropical, splenectomy

Malaria is a major medical problem in many parts of the world. It has become even more important in recent years because of the development of parasite resistance to antimalarial drugs, and because of an increase in the amount of international travel. Chloroquine-resistant *Plasmodium falciparum* emerged in the early 1960s in South East Asia and Central America, became established in East Africa in the late 1970s, and in recent years has spread to West Africa[1]. The seriousness of the problem is illustrated by the remark that 'history has demonstrated only too clearly the ease with which *P. falciparum* can become resistant to any antimalarial to which it is exposed'[1]. Just as we were reassured that 'the problem of drug resistance is limited to *P. falciparum*'[1], the first reports were appearing from Australasia of chloroquine-resistant *P. vivax*[2,3]. An effective antimalarial vaccine still appears to be many years away[4]

Meanwhile, malaria is encountered with ever-increasing frequency in non-endemic areas[5]. There has been a marked increase in the number of *P. falciparum* infections in the UK in recent years[6], and in 1987 alone 1.6 million British citizens visited malarious areas[7]. A recent study showed a serious lack of appreciation of the dangers of malaria among travel clinic attenders[8].

For the surgeon working in parts of the world where malaria is endemic, the disease may be important at all stages of management. Chronic malaria may affect the patient's preoperative status, and malaria may complicate the postoperative course Occasionally the surgeon may be called upon to perform splenectomy for tropical splenomegaly. The risks of malaria in addition to bacterial infections make splenic conservation highly desirable whenever possible after rupture of the spleen, be it traumatic or spontaneous. Malaria may also complicate blood transfusion.

It is clear that modern surgeons, wherever their practice or whatever their specialty, require more than a superficial knowledge of malaria. This report reviews those aspects of malaria considered to be of importance to surgical practice.

Malaria and splenic rupture

The relationship between malaria and rupture of the spleen is a complex one. Non-traumatic rupture of the spleen has been classified as spontaneous (when the spleen is normal) and pathological (when the spleen is diseased)[9]. The distinction between non-traumatic rupture and rupture following trivial trauma is often impossible and is largely irrelevant[9,10]. Pathological rupture of the spleen is well described in malaria but is rare. Malaria is, however, the commonest cause of pathological rupture, and it was responsible for 22 of the 39 cases reported by Smith and Custer[11]. Other causes include infectious mononucleosis, congestive splenomegaly, and leukaemia[9,11]

It is the patient with low immunity or no immunity to malaria who is most at risk of rupture. Of the 64 cases reviewed by Hershey and Lubitz[12], 39 occurred as a result of induced malaria, which was commonly used at the time as treatment for neurosyphilis. Clezy and Richens[13] described spontaneous rupture of a malarial spleen in a patient from Papua New Guinea She came from a highland region where malaria was rare and immunity to it was generally absent Although rupture generally occurs during an overt attack of malaria, Bearn[14] reported a case occurring in an apparently well man (who did however develop overt malaria two days after splenectomy). The formation and subsequent rupture of a subcapsular haematoma is believed to be the usual mechanism involved[12,14,15].

Whether or not the enlarged spleen of chronic malaria is more prone to rupture than a normal spleen is disputed. Although it is commonly stated that the pathologically enlarged spleen is more prone to rupture[16], and that the enlarged malarial spleen shares this risk[17], there is little hard evidence to support this assumption Some believe that, as well as being larger, the malarial spleen is tougher[13] Crane *et al.*[18] found no case of traumatic rupture of the spleen in their follow-up of 75 patients with tropical splenomegaly in Papua New Guinea. A more recent report from the same country[19] found that 54 per cent of splenic ruptures were caused by assault, compared with 15 per cent by motor vehicle accidents, but this may be a reflection of traffic density and accident rates rather than any tendency for the spleen to be ruptured by less severe trauma.

Traumatic rupture of the spleen in the tropics

Traumatic rupture of the spleen is common in many tropical countries[19] and the incidence may be increasing[20] The infectious complications of splenectomy are now well recognized[21], and the importance of splenic preservation whenever possible is generally accepted[22]. Splenectomy increases susceptibility to pneumococcal infections, and also to infections with *Haemophilus influenzae*, *Neisseria miningitidis*, and many other bacteria[21]. Infections with these organisms are common in the tropics. Splenectomy may also alter the immune response to schistosoma[23]

The intact spleen plays a central role in the body's defence

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against malaria[24,25]. There are numerous clinical reports of unusual or severe malaria following splenectomy. Maharaj *et al.*[26] described a patient who developed severe malaria complicated by renal failure despite regular antimalarial prophylaxis. He had undergone splenectomy 20 years previously. Israeli *et al.*[27] described falciparum malaria in an asplenic man whose blood smear showed all the developmental stages of the parasite. Tsuchida *et al.*[28] reported postoperative malaria in a man undergoing nephrectomy and splenectomy 36 years after his original infection, and Watson-Williams and Allan[29] reported fatal cerebral malaria in a 45-year-old indigent African 9 months after splenectomy.

It is clear that splenic preservation is particularly desirable in the tropics, and in patients who intend to go to or return to the tropics. A group of interested surgeons in Papua New Guinea have practised a policy of conservative management of traumatic rupture of the spleen with good results. Thus, Hamilton and Pikacha[17] were able to preserve the spleen in 26 of 43 patients admitted under their care, and all but three of these 26 were successfully managed without surgery. Of those who underwent splenectomy, one was known to have subsequently died of cerebral malaria. A more recent report from the Papua New Guinea Splenic Injury Study Group[19] described a series of 205 adults treated for ruptured spleen. Initial non-operative management was attempted in 137 cases, and was successful in 110 (80 per cent). The incidence of associated intra-abdominal injury was low in this series (14 patients) and probably reflects the predominant mechanism of injury, assault accounting for 54 per cent of cases. Even in those who required laparotomy, splenorrhaphy was possible in 26 patients. Delayed rupture of the spleen was not seen after non-operative management in either of these two series. One well recognized complication following successful non-operative management is the occurrence of post-traumatic splenic cysts[19]. Although in the past splenectomy has been recommended[30], splenic preservation is possible by either partial splenectomy[31] or partial excision and drainage of the cyst[32].

Despite the advisability of avoiding splenectomy whenever possible, the lack of trained surgeons, poor nursing facilities, and the absence of a blood bank may militate against a selective non-operative approach in many areas[20]. Nevertheless, even if facilities are considered inappropriate for non-operative management, repair of the spleen at laparotomy should be considered. The value of autotransfusion in such cases should not be forgotten When splenectomy proves unavoidable, patients should be advised to take antimalarial prophylaxis for life, although compliance is often poor[17].

Tropical splenomegaly syndrome

Tropical splenomegaly syndrome is an incompletely understood condition found only in areas where malaria is endemic It is characterized by massive splenomegaly (palpable tip usually at or below the level of the umbilicus), and is associated with hypersplenism, elevated IgM levels, hepatic lymphocytic infiltration and a high titre of malarial antibodies. Malarial pigment is scanty or absent in liver and spleen, and parasitaemia is difficult to demonstrate[33] The association with a high malarial antibody titre[33–35] and the response to antimalarial treatment[29,36–38] has led to the suggestion that the disorder represents an atypical immune response to malaria[39] – indeed, it is sometimes now referred to as hyper-reactive malarial splenomegaly[40]. Although Ziegler *et al.*[41] found no evidence of any generalized impairment of cellular or humoral immunity in these patients, it has been suggested that they are unduly susceptible to overwhelming bacterial infection[18]. Untreated, the disorder is progressive and there is a definite but ill-defined risk of the development of malignant lymphoreticular disease[36,37,42]. Whether treatment alters this risk is unclear. Despite the large spleen size, these patients do not appear to be at greater risk of traumatic rupture of the spleen[18].

There are two approaches to management: medical and surgical. Medical therapy consists of long-term antimalarial treatment[29,36–38]. Improvement is often slow, and it may take up to 1 year for the maximum benefit to be apparent[29]. Hepatosplenomegaly regresses, anaemia improves, and IgM levels fall. In one series, failure to respond was associated with the subsequent development of malignant lymphoma or leukaemia[36]. Prolonged antimalarial therapy in these patients is not without risk, and a decline in host defences may accompany the fall in γ-globulin[43]. Cessation of therapy may be hazardous, and clinical relapse occurs rapidly.

Splenectomy has also been advocated[42], and it also reverses haematological abnormalities as well as improving patients' general sense of well-being. Its disadvantages include operative mortality and an increased risk of lethal bacterial infection. Severe and sometimes fatal malarial infection may also occur Crane *et al.*[44] studied the long-term results of splenectomy in New Guinea and found that seven of the 18 surgical survivors had died after short illnesses. Although the long-term mortality rate after splenectomy was lower than that associated with no treatment, these authors felt that splenectomy should be abandoned in favour of antimalarial treatment. Hamilton *et al.*[45] followed three patients treated by splenectomy for 5 years. They found progressive hepatomegaly and persistent abnormalities on liver biopsy, and concluded that splenectomy does not alter the basic stimulus to reticuloendothelial hypertrophy, as does antimalarial treatment. Surgery should therefore be reserved for those who fail to respond to medical treatment. Although advocating surgery also for those with disabling symptoms, Pryor[46] noted that despite gross splenomegaly and considerable anaemia, most patients with tropical splenomegaly syndrome are not greatly disabled. Even after splenectomy, these patients should take regular and probably lifelong antimalarial prophylaxis[45].

Transfusion malaria

Although the risks of acquiring hepatitis B and human immunodeficiency virus infection by blood transfusion are well known, malaria may also be transmitted by blood transfusion. Infection is often severe, partly because of delay in diagnosis, and transmission may occur after transfusion of whole blood or blood components[47].

In non-endemic countries, transfusion malaria is rare. Although a recent report from Kuwait[48] estimated the rate of risk of transfusion malaria to be 79 per million units drawn, the rates are considerably lower in most developed countries. There were only 26 cases recorded in the USA from 1972 to 1981, a rate of 0·25 per million donor units collected[49]. However, four of these patients died as a result. In half of the cases where a specific infective donor could be identified recent residence in or travel to a malarious area should have resulted in exclusion. Identification of infective donors may be difficult as they are often asymptomatic and have very low levels of parasitaemia[47,49]. The minimum infective dose is very small[50]. Screening by blood smear is ineffective, and screening by serology not cost-effective in areas where the risk of transmission is low. Careful history taking should identify potentially infective donors, i.e. those who were born in, resident in, or have travelled in endemic areas. Screening this group by serological tests may be useful to exclude infected donors[47,48], and indeed as a basis for accepting those found to be negative[51].

A study in Colombia[52] using the ELISA (enzyme-linked immunosorbent assay) technique for detecting malarial antibodies found positive results in 8·6 per thousand serum samples However, in most countries where malaria is prevalent, detection and exclusion of parasitized donors is often impossible[53]. Instead, reliance is placed on chemoprophylaxis of donors[47] or recipients[53]. Although difficulties may be encountered in areas of drug resistance, in practice these methods are often very effective[50]

Health care workers in non-endemic areas should also be aware of the possibility of malaria transmission by accidental contamination with infected blood, as a number of recent reports have illustrated[54,55]

Postoperative malaria

It is widely held that surgery may precipitate a relapse of malaria[56] but the evidence is scanty. Kark[57] studied postoperative malaria in British troops during World War II and questioned the role of surgery in precipitating malarial relapse. The overall incidence of relapse was 10 per cent, there were no differences in the rates following major and minor surgery, and the incidence was comparable to that in non-surgical patients. Simpson[58] described the failure of a variety of non-surgical stress measures to provoke relapse in *P. vivax* infection, and Bruce-Chwatt[59] reviewed the lack of evidence for precipitation of relapse by major surgery. Splenectomy and pregnancy have been clearly shown to exacerbate malaria, and both are associated with a sudden change in immunological balance[59]. Even when malaria does occur in the postoperative period, it is difficult if not impossible to be certain that its occurrence was precipitated by surgery[57,60,61].

Ajao's study[62] is often quoted. He found that 49 per cent of postoperative fevers were caused by malaria. However, the diagnosis was based largely on a positive thick blood smear; the level of parasitaemia was not documented, and no control groups (non-operated patients or afebrile surgical patients) were studied. He advised routine chloroquine prophylaxis before surgery. Nevertheless, many postoperative fevers are transient and settle spontaneously, so that response to antimalarial treatment does not prove a malarial aetiology. More importantly, in semi-immune patients living in malaria endemic areas, the finding of a positive blood smear alone[63] is not enough to establish a diagnosis, unless the level of parasitaemia is considered[64]. A study from Brazzaville[65] found that 80 per cent of unselected subjects between 1 and 14 years of age had positive smears, the rate declining to 36 per cent in people over 40 years of age.

In 1977 Eykyn and Braimbridge[66] described three patients from Tanzania who developed *P. falciparum* malaria following open heart surgery in the UK. Transfusion malaria appeared to be out of the question. However, the nature of the surgery, with its necessity for transfusion, might suggest another mechanism. Blood transfusion has recently been shown to affect outcome following cancer surgery adversely[67], and it may also increase infectious complications after such surgery[68] An immunosuppressive mechanism is thought to be important. Whether transfusion might also precipitate malarial relapse remains speculative but deserves further study

Despite the lack of firm evidence of benefit, routine antimalarial prophylaxis after major surgery is practised in many areas[56]. Perhaps it would be wiser to limit such a policy to selected patients, e.g. those undergoing splenectomy, the pregnant and patients who have received or may receive blood transfusion. Using prophylaxis to 'exclude malaria in the differential diagnosis of postoperative fever'[56] is less valid, particularly in areas where drug-resistant strains are prevalent.

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Pylorus preserving pancreatoduodenectomy: an overview

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Pylorus preserving pancreatoduodenectomy (PPPD) was reintroduced 12 years ago. Since that time, over 400 patients have undergone PPPD with approximately 41 per cent having chronic pancreatitis and 54 per cent having pancreatic and other periampullary malignancies. Reported 5-year survivals in this latter group have been comparable to those achieved by the classic Whipple procedure. The postoperative mortality rate in 339 reported patients has been 3·8 per cent. Postoperative morbidity, including delayed gastric emptying, has been similar to that of the classic Whipple operation. However, PPPD has been associated with fewer late problems with dumping, diarrhoea, delayed gastric emptying (8·6 per cent), and marginal ulceration (3·6 per cent). Moreover, most patients undergoing PPPD have been able to return to their preoperative and preillness weight. The additional advantage of decreased operative time makes PPPD an attractive alternative to the classic pancreatoduodenectomy.

Keywords: Pancreatoduodenectomy, chronic pancreatitis, pancreatic carcinoma, ampullary carcinoma, distal bile duct carcinoma, duodenal carcinoma

The incidence of pancreatic cancer and periampullary tumours has increased steadily over the last 40 years[1] while chronic pancreatitis, although an uncommon condition[2], continues to pose a major therapeutic challenge to the surgeon[3] In recent years a variety of new surgical approaches to pancreatic resection have been developed. These approaches range from the radical regional pancreatoduodenectomy advocated by Fortner[4] to the pylorus preserving pancreatoduodenectomy (PPPD) and duodenal preserving pancreatectomy popularized by Longmire[5] and Russell[6], respectively. Local excision of periampullary carcinomas has also had its advocates in recent years[7]. The purpose of the present analysis is to review the impact of PPPD on pancreatic surgery since its reintroduction 12 years ago.

Historical development

While there are several reports of pancreatoduodenal resections from the end of the 19th and the beginning of the 20th centuries[8–12], it was not until 1935 that the modern era of pancreatic surgery was inaugurated. In that year Whipple, Parsons and Mullens[13] published their report of the first successful two-stage radical pancreatoduodenectomy for periampullary carcinoma. In the first stage of the operation, the patient underwent a gastrojejunostomy, ligation of the distal common bile duct and cholecystogastrostomy. Subsequently, the second part of the duodenum, the ampulla of Vater, the adjacent head of the pancreas and the distal common bile duct were removed, and the pancreatic stump was oversewn. Thus, the antrum and pylorus were structurally preserved as a blind stump, and the patency of the gastrointestinal tract was restored by a gastroenterostomy.

In 1941 Trimble *et al.*[14] advocated resection of the distal stomach with a Pòlya antecolic anastomosis, eliminating the blind pyloric stump and the suture line in the duodenum, a potential source of leakage. Whipple also advocated distal gastrectomy and a choledochojejunostomy, and both Whipple and Trimble independently reported successful one stage radical pancreatoduodenectomy in 1941[14,15]. In 1944 Watson[16] described a pancreatoduodenectomy for carcinoma of the ampulla of Vater in which he preserved the antrum, pylorus, and 1 inch of duodenum. He re-established alimentary continuity with a duodenojejunostomy thus preserving in functional continuity the antrum, pylorus, and first part of the duodenum. Watson believed that preservation of the stomach would lead to better digestion and that a duodenojejunostomy would prevent anastomotic ulceration. To Watson, therefore, must go the credit for describing the first PPPD Watson's report, however, was forgotten, and gastric resection with or without vagotomy became an integral part of the standard 'Whipple' operation[17–20]. The rationale for inclusion of gastrectomy and vagotomy has been to prevent marginal ulceration and to provide adequate margins when resecting tumours This operation continues to be the most frequently performed operation for resectable lesions in the head of the pancreas.

In 1978 Traverso and Longmire[5] revived the idea of preserving the pylorus during pancreatoduodenectomy They reported two patients in whom the stomach, pylorus, and first part of the duodenum were preserved and alimentary tract continuity was re-established by end-to-side duodenojejunostomy. These authors, like Watson, reasoned that preservation of the stomach and pylorus would eliminate the complications of a reduced gastric reservoir and improve gastrointestinal function. They also believed that preserving the pylorus would prevent exposure of the jejunum to excessive amounts of acid, thereby reducing the incidence of jejunal ulceration. Furthermore, they argued that resection of the distal stomach, pylorus, and proximal duodenum was unnecessary in the management of benign disease[5].

Indications and survival

Traverso and Longmire[5] initially performed PPPD in two patients One had chronic pancreatitis with associated pseudocyst formation in the head of the pancreas while the

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Table 1 *Indications for pyrlous preserving pancreatoduodenectomy*

Authors (reference)	Year	No of patients	Chronic pancreatitis	Malignancy	Other
Watson[16]	1944	1	0	1	0
Gall *et al*[21]	1982	18	18	0	0
Mosca *et al.*[22]	1984	30	8	22	0
Flautner *et al.*[23]	1985	37	37	0	0
Warshaw and Torchiana[24]	1985	8	4	4	0
Pearlman *et al*[25]	1986	6	1	5	0
Itani *et al*[26]	1986	7	1	5	1
Crist *et al*[27]	1987	14	0	14	0
Eck and Murry[28]	1987	2	0	2	0
Kim *et al.*[29]	1987	13	6	4	3
Braasch *et al.*[30–33]	1988	126	41	82	3
Williamson and Cooper[34–36]	1988	31	17	13	1
Longmire *et al*[5,37–40]	1988	46	13	28	5
Hunt and McLean[41]	1989	16	5	9	2
McAfee *et al*[42]	1989	33	12	18	3
Sharp *et al*[43]	1989	6	0	6	0
Total		394	163 (41)	213 (54)	18 (5)

Values in parentheses are percentages

second had a small localized carcinoma of the third part of the duodenum Over 160 patients have since undergone PPPD for chronic pancreatitis (*Table 1*)[21–42]. Braasch and his colleagues[30–33] at the Lahey Clinic advocate the pylorus preserving operation in all resections of the right side of the pancreas for chronic pancreatitis except those patients with duodenal ulcer disease. However, the presence of pancreatitis throughout the gland requiring total pancreatectomy has also been combined with PPPD[24,38]. The advantages of pylorus preservation in these patients are that the patient can eat normal sized meals, and the absence of gastrectomy diminishes the risk of the dumping syndrome[3]

Doubts have been raised as to the advisability of performing the pylorus preserving operation for malignant disease in the periampullary area, as the field of resection may be reduced and survival thereby compromised[43,44]. Moossa[45] has argued that the pylorus preservation procedure is not applicable to cancer of the head of the pancreas or distal common bile duct tumours since it may compromise the only chance of cure in these patients Sharp and his colleagues[43] have also reported tumour recurrence at the duodenal suture line. However, Newman and associates[30] have observed that the other resection margins in pancreatoduodenectomy are much closer to the tumour than the duodenum and antrum. Performing frozen section of the duodenal resection margin should also minimize this problem Therefore, leaving the antrum, pylorus, and first few centimetres of the duodenum is unlikely to compromise the field of resection. Moreover, several recent reports contain details of patients who underwent PPPD for a variety of periampullary malignant lesions including ductal pancreatic carcinoma with excellent long-term survival[22,24–43].

A total of 213 pancreatoduodenectomies have now been reported for malignant periampullary disease (*Table 1*). Braasch and associates[30–32] have reported actuarial 5 year survival rates of 65 per cent for ampullary adenocarcinoma, 45 per cent for bile duct carcinoma, and 20 per cent for adenocarcinoma of the head of the pancreas following PPPD. These figures compare favourably with published survival rates following the standard Whipple resection: 37 per cent[46] to 60 per cent[47] for ampullary carcinoma; 17 per cent[46] to 30 per cent[32] for carcinoma of the distal common bile duct; and 6 per cent[46–48] to 18 per cent[27] for pancreatic adenocarcinoma.

In a previous analysis from the University of California at Los Angeles, the present authors compared survival in a group of 26 patients with histologically proven adenocarcinoma of the head of the pancreas who were treated with either a PPPD $(n=13)$ or a classical Whipple resection $(n=13)$[39] The two groups of patients were comparable in terms of age, sex, preoperative laboratory data, and tumour staging The actuarial survival rate was 25 per cent at 5 years for the pylorus preserving group compared with 12 per cent at 3 years for the classic Whipple group. Thus, patient survival appears not to be compromised following PPPD for adenocarcinoma of the head of the pancreas. We, therefore, agree with Braasch and co-authors who advocate PPPD in all patients with pancreatic and periampullary tumours except those cancers of the duodenum or bile duct that are in close proximity to the first centimetre of the duodenum[31,32].

Operative technique

Adequate exposure is essential for assessment of resectability of the pancreas and subsequent pancreatoduodenectomy. The head of the pancreas is best approached through a right subcostal incision. This incision can easily be converted to a bilateral subcostal incision if a resection is to be undertaken. In a thin patient with a narrow costal angle, a midline upper abdominal incision also provides good exposure. In a patient with malignant disease, a full and comprehensive laparotomy is performed initially to detect metastases in the liver, lymph nodes, peritoneum, or omentum. A Kocher manoeuvre is performed and the head of the pancreas evaluated for size and location of the primary lesion. Invasion of contiguous structures such as the portal or superior mesenteric veins, the superior mesenteric artery, and the common hepatic artery can now also be assessed

If a preoperative histological diagnosis has not been made, biopsy of the primary lesion and any lymph nodes can be undertaken Biopsy material can be obtained by open scalpel biopsy of any superficial lesion, transduodenal Tru-Cut® needle (Travenol Laboratories Inc , Deerfield, Illinois, USA) biopsy of the pancreatic mass or fine needle aspiration cytology of the lesion. The common duct may also be opened and curettage biopsy material obtained from the distal common bile duct. Controversy exists, however, as to whether histological proof of carcinoma of the head of the pancreas is necessary before embarking on pancreatoduodenectomy Longmire and Traverso[20] have suggested that if the possibility of a resection for benign disease has been discussed with the patient, it is acceptable to perform pancreatectomy without tissue diagnosis Thus, a potentially curable occult lesion is not overlooked. Others have argued that if pancreatitis is severe enough to be confused with malignancy, pancreatectomy is probably indicated in any case[49].

An assessment of resectability is now undertaken. The dissection is carried along the third part of the duodenum to expose the superior mesenteric vein at the point where it crosses the duodenum and passes under the neck of the pancreas A critical determination of resectability is the ability to separate the portal and superior mesenteric veins from the adjacent pancreas. Major tributaries usually do not enter the portal vein on its ventral surface behind the pancreatic neck, and it should be possible to develop a plane between these two structures If this manoeuvre can be achieved, resection is usually feasible.

An intact neurovascular supply to the pylorus and the first part of the duodenum is essential for the success of the pylorus preserving operation. The right gastric artery is preserved, and the gastroduodenal artery is isolated and divided at the junction with the hepatic artery. The gastroepiploic vessels along the entire greater curvature of the stomach are carefully preserved as is the vagal innervation of the pylorus and antrum. The right gastroepiploic artery is divided at its origin from the anterior pancreaticoduodenal artery on the head of the pancreas (*Figure 1*).

The common hepatic duct should be divided just proximal to the cystic duct and a cholecystectomy performed. The duodenum is divided 2 cm distal to the pylorus. Unless a total pancreatectomy is being undertaken, the pancreas should be transected across the surgical neck. Transfixion sutures placed along the upper and lower margins of the pancreas on either side of the line of transection will reduce bleeding from the cut surface of the pancreas. Division of the small bowel distal to the ligament of Treitz will facilitate dissection of the uncinate process. Division of arterial and venous branches close to the jejunum at the ligament will help to avoid injury to the superior mesenteric artery. Bringing the divided jejunum to the patient's right at this stage is also often a helpful manoeuvre The uncinate process should now be carefully dissected from behind the superior mesenteric vein. Several small veins in this region must be individually ligated. The uncinate process may now be freed completely by dividing the remaining retroperitoneal tissues and branches to the superior mesenteric artery

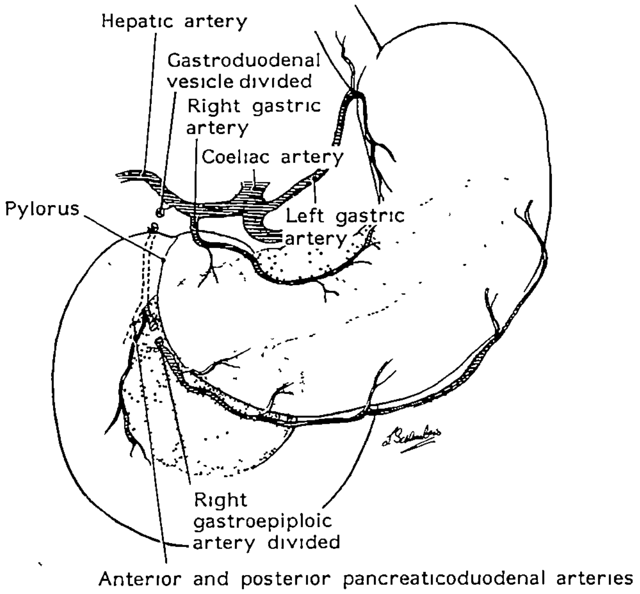
Hepatic artery
Gastroduodenal vesicle divided
Right gastric artery
Coeliac artery
Pylorus
Left gastric artery
Right gastroepiploic artery divided
Anterior and posterior pancreaticoduodenal arteries

Figure 1 *Preserving the blood supply to the pylorus. The right gastric artery is preserved. The gastroduodenal artery is divided at its junction with the hepatic artery. The right gastroepiploic artery is divided at its origin from the anterior pancreatoduodenal artery preserving the gastroepiploic vessels along the greater curvature of the stomach. (from Grace* et al.[39])

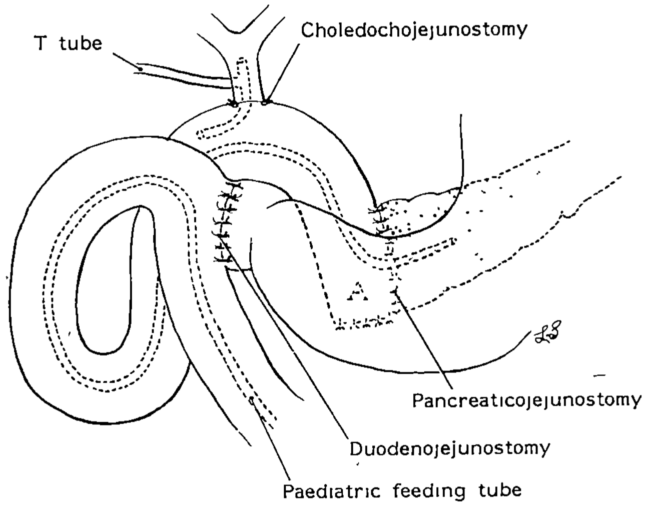

Figure 2 *End-to-side duodenojejunostomy with the pancreaticojejunostomy and choledochoduodenostomy placed proximally A long paediatric feeding tube splints the pancreatojejunal anastomosis (from Grace* et al.[39])

Reconstructive methods

Reconstruction of the alimentary tract is now undertaken. Two different methods of duodenojejunostomy have been described. Watson performed an end-to-end duodenojejunostomy in his operation[16], a technique also favoured by Flautner and colleagues[23], while Traverso and Longmire[5] described an end-to-side anastomosis of the duodenal segment to a loop of jejunum. A variety of methods of managing the pancreatic stump have also been advocated. These include ligation of the pancreatic stump[16], pancreatic duct occlusion[50], pancreaticojejunostomy[5], and pancreaticogastrostomy[23,51]. Pancreatic duct ligation is not to be recommended as it leads to a high incidence of fistula formation[52,53]. Pancreatic duct occlusion also has the long-term problem of assuring pancreatic exocrine insufficiency and the need for enzyme replacement.

To help neutralize gastric acid, the pancreaticojejunostomy and the choledochojejunostomy are placed proximal to the duodenojejunostomy. Placing the pancreaticojejunostomy proximal to the choledochojejunostomy also facilitates reoperation if resection is required for a leak at the pancreaticojejunostomy. A number of methods of pancreaticojejunostomy are available. If the pancreas is soft with a small pancreatic duct, as is often the case with malignant disease, the transected pancreatic stump can be invaginated into the proximal jejunum. This procedure is called the 'dunking' pancreaticojejunostomy and was originally described by Desjardins in 1907[9] However, if the duct is dilated and thickened from chronic pancreatitis, a mucosa-to-mucosa anastomosis between the pancreatic duct and the jejunum should be performed (*Figure 2*)[54]. Either an end-to-side or lateral pancreaticojejunostomy as described by Traverso and Longmire[5] in their patient with pancreatitis can be undertaken. Stenting this anastomosis may reduce the incidence of postoperative pancreatic fistula[38]. Braasch and co-workers have indicated that in patients who do not have chronic pancreatitis long-term patency of the pancreatic anastomosis may be better following the dunking procedure than after the end-to-side anastomosis[31].

Recently, a number of authors have advocated pancreatogastrostomy as an ideal complement to PPPD for chronic pancreatitis[23,51,55]. Flautner and his colleagues[23] argue that pancreatogastrostomy is technically easier than pancreatojejunostomy and that during the postoperative period the anastomosis may be easily examined by endoscopy or radiology. Furthermore, the alimentary tract is restored so that a blind intestinal segment does not remain. Recent evidence also suggests that pancreatogastrostomy may give better relief of pain than pancreatojejunostomy in patients with chronic pancreatitis[55]. This procedure has the significant potential disadvantage, however, of leading to both a pancreatic and gastric fistula when an anastomotic leak occurs Whenever possible, a small plastic catheter should be placed into the pancreatic duct to act as a splint for the pancreatic anastomosis. An end-to-side choledochojejunostomy is then created Soft, closed suction drains are placed adjacent to the pancreatic and biliary anastomoses before closing the abdomen.

Postoperative mortality

In recent years, a substantial improvement in operative mortality has been reported following pancreatoduodenectomy. Twenty-two years ago, Howard[56] was able to report 41 consecutive Whipple procedures without mortality. However, his experience was unique as contemporary reports recorded operative mortality rates of 20–40 per cent[57–59]. During the last decade, operative mortality rates decreased to 10–12 per cent in tertiary referral centres[52,60,61]. However, Herman in 1978[62], combining the results of 1005 Whipple procedures performed by 18 surgeons, reported an overall surgical mortality rate of 20 per cent. Current reports suggest that pancreatoduodenectomy carries an operative mortality rate of less than 5 per cent[27,38,63,64]. PPPD is associated with comparable operative mortality rates Among 339 patients in the recent literature, 13 perioperative deaths were reported for an operative mortality rate of 3·8 per cent (*Table 2*)[21–28,30–35,41–43]. However, only two of the deaths were procedure related. One patient died following dehiscence of the duodenojejunal anastomosis[22] while the second patient died following a pancreatic fistula[34]. Furthermore, the reported incidence of pancreatic fistula[31,34,38,39], biliary fistula[31,39], and enteric fistula[22] following PPPD is in the same range as after the classic Whipple procedure Moreover, these reports indicate that PPPD is a safe operation carrying with it a low operative mortality.

Gastric and small bowel function

One of the concerns expressed about the pylorus preserving operation has been whether the stomach would empty satisfactorily following the procedure. In reviewing the collected experience of 284 patients, transient delay in gastric emptying was found to occur in 27·1 per cent of patients (*Table 2*)[22–24,27,30,31,34,38,39,41,42] Braasch and his colleagues[31] noted that 50 per cent of their patients required gastric suction for more than 7 days. Similarly, Warshaw and Torchiana[24] observed a significant delay in achieving full diet in patients following the pylorus preserving procedure compared with the classical Whipple procedure (16 days *versus* 9·8 days). Mosca and his colleagues[22] reported the resumption of normal gastrojejunal emptying around the tenth postoperative day, while 8 days was the longest period of nasogastric aspiration in Williamson and Cooper's experience[35].

In a previous analysis, however, the present authors found that postoperative nasogastric intubation was required for a similar period in both pylorus preserving (6·7 days) and classical Whipple (7·7 days) patients[38]. A recent study from Johns Hopkins also failed to observe any difference in the incidence of delayed gastric emptying between patients undergoing the pylorus preserving procedure or partial gastric resection (29 *versus* 28 per cent)[27]. Similarly, McAfee *et al.*[42] from the Mayo Clinic found no differences between the PPPD and the classic Whipple operation with respect to mean days of nasogastric suction (7·6 *versus* 7·9) or percentage of patients with early gastric stasis (28 *versus* 33 per cent). Moreover, Hunt and McLean[41] have suggested that delayed gastric emptying in the early postoperative period is usually associated with another intra-abdominal complication In the authors' experience early delayed gastric emptying is most often associated with a leak at the pancreatojejunal anastomosis or with postoperative pancreatitis.

Table 2 *Postoperative mortality and morbidity rates*

	No of patients	Total
Postoperative mortality rate	13	339 (3·8)
Delayed gastric emptying rate		
Postoperative	77	284 (27·1)
Long-term	5	58 (9)
Marginal ulceration rate	12	331 (3·6)

Values in parentheses are percentages

Several investigators have studied gastric function in detail following pylorus preserving pancreatectomy in both humans and experimental animals. Traverso and Longmire[37], in a detailed study of gastric function using pyloric fluoroscopy and gastric barium emptying, found normal gastric emptying in all eight patients studied 2 to 12 months following pancreatic resection. Braasch and colleagues[31] using isotopes to measure gastric emptying of liquids and solids found no differences between five control subjects and five patients following PPPD. Patti and co-workers[65] in San Francisco measured gastric emptying and small bowel transit in ten patients following PPPD They found that the rate of gastric emptying was normal in six patients, faster than normal in three, and abnormally slow in a single patient who was subsequently found to have diffuse carcinomatosis. Small bowel transit was found to be increased in seven patients, which Patti and his associates attributed to loss of exposure of the duodenum to food.

Recent studies by Fink *et al.*[40] by Hunt and McLean[41], and by Cooper *et al.*[66] confirm that the majority of patients have normal gastric emptying after PPPD. In comparison with patients undergoing the classic Whipple procedure, Cooper *et al.*[66] found no significant differences. In the study by Fink and his colleagues[40], gastric emptying of liquids was normal after PPPD but delayed after the standard Whipple. Thus, of 58 patients without recurrent cancer who have had gastric emptying studies many months after surgery, only five (9 per cent) have had delayed emptying (*Table 2*)[31,37,40,41,65,66].

Itani and colleagues[67] studied the effects of duodenojejunostomy on gastric emptying and on gastric motility in dogs. These investigators found no significant difference in gastric emptying in either control or duodenojejunostomy animals during the 3-month period of observation. Similarly, gastric myoelectric activity was unaltered by duodenojejunostomy. PPPD does not remove the natural duodenal pacemaker which is located approximately 0·5 cm distal to the pylorus[68]. Altered small bowel motility has been demonstrated in patients following the classic pancreatoduodenectomy[69]. However, dumping and diarrhoea have not been long-term problems following PPPD.

Despite normal gastric myoelectric activity, Itani and colleagues[67] observed profound alterations in proximal small bowel myoelectric activity following duodenojejunostomy in dogs. Specifically, they observed a significant decrease in pacesetter potential frequency in the bowel distal to the site of duodenal transection. The physiology of gastrointestinal motility following PPPD remains to be completely elucidated The role of hormones, gut peptides, and neurological factors in the regulation of gastrointestinal motility following pancreatoduodenectomy needs further study The evidence to date supports the view that in the majority of patients no significant long-term alterations in upper gastrointestinal motility occur following PPPD. Although delayed gastric emptying may be seen in a quarter of the patients in the early postoperative period, this problem is often related to a pancreatic fistula or pancreatitis.

A number of investigators have observed enterogastric reflux in some patients following PPPD Braasch *et al.*[31] using ^{99m}Tc bound to iminodiacetic acid calculated an enterogastric reflux index which reflected the percentage of pancreatobiliary and jejunal contents that reflux into the stomach over a period following injection of the isotope Although two of five patients showed evidence of reflux, they noted a wide divergence of reflux values following pyloric preservation. The other three patients studied had reflux curves similar to normal controls. Mosca and his colleagues[22] in an analysis of 14 patients post-pylorus preservation recorded biliogastric reflux in six patients. However, in only two patients was reflux marked and prolonged. Cooper *et al.*[66] have also documented that enterogastric reflux is more common after the classic Whipple procedure than after PPPD Braasch[32] has even suggested that preservation of the pylorus by preventing alkaline reflux and antral stimulation may prevent peptic ulcer formation. However, the significance of reflux in patients following pylorus preservation is difficult to determine as it has been postulated that duodenogastric reflux is a physiological phenomenon in man[70] Moreover, Fink and associates[40] found no mucosal lesions in their PPPD patients who underwent postoperative endoscopy.

Marginal ulceration

Marginal ulceration has posed a considerable problem following classic pancreatoduodenectomy Owens in 1948[71] reported three patients with peptic ulcer following Whipple operations and advised that the gastroenterostomy should be placed distal to the pancreatic and biliary anastomoses. Ten years later, Porter reported three marginal ulcers which occurred despite distal placement of the gastroenterostomy[72]. He advocated hemigastrectomy for prevention of the problem while Elliot[73] argued that pancreatoduodenectomy inevitably led to gastric hyperacidity unless an antrectomy was performed.

Grant and van Heerden[18] in an analysis of 297 patients who had undergone pancreatoduodenal resection at the Mayo Clinic observed anastomotic ulceration in 18 patients (6 per cent) of whom seven had undergone total pancreatectomy These authors observed that total pancreatectomy was more ulcerogenic than a Whipple procedure and that a 50 per cent gastric resection was inadequate to prevent marginal ulceration. In an attempt to reduce the incidence of anastomotic ulceration, Scott and his colleagues[19] advocated truncal vagotomy with pancreatoduodenectomy. In an analysis of 41 pancreatoduodenectomies, they observed anastomotic ulceration in 36 per cent of patients without vagotomy compared with no ulceration in patients who had undergone vagotomy However, Walsh and associates[74] found that antrectomy alone was associated with a marginal ulcer rate of 12 per cent compared with 9 per cent when vagotomy was added These findings have since been substantiated by Grace and associates[38] and Crist and colleagues[27] who found that the incidence of marginal ulceration was similar for antrectomy alone or antrectomy plus vagotomy

Watson[16] and Traverso and Longmire[5] believed that preserving the pylorus during pancreatic resection would decrease the postoperative incidence of jejunal ulceration The clinical experience to date would support their hypothesis. Braasch and associates[33] in their series of 126 patients reported six patients (5 per cent) in whom the diagnosis of marginal ulceration was suggested either radiologically or by endoscopy Four patients were managed successfully by medical means while two underwent operation. Grace *et al.* observed no upper gastrointestinal bleeding in the immediate postoperative period in 39 patients following PPPD, but two patients (5 per cent) presented at 16 and 61 months after operation. One was found to have a marginal ulcer which required gastric resection while the other had non-specific upper gastrointestinal bleeding probably related to portal hypertension. In a later follow-up of this series by Fink *et al*[40] two of 46 patients (5 per cent) had developed marginal ulceration.

All 30 patients in the series by Mosca *et al*[22] underwent upper gastrointestinal endoscopy. Five patients had moderate inflammation of the antral mucosa but in no patient was marginal ulceration demonstrated Similarly, neither Flautner and his associates[23], Perlman and his colleagues[25], nor Kim *et al*[29] reported marginal ulceration in a total of 60 patients. Crist and colleagues[27] reported a single case of upper gastrointestinal bleeding following PPPD among 14 patients (7 per cent) Warshaw and Torchiana[24] observed a single case of jejunal ulceration in their series of eight patients (12 per cent). This patient required antrectomy and vagotomy McAfee *et al.*[41] reported marginal ulceration in four of 31 patients (13 per cent) Hunt and McLean[41] have reported the highest incidence of marginal ulceration with three of 16 patients (19 per cent) developing this problem

Thus, of 331 patients who have undergone PPPD, twelve (3·6 per cent) have had postoperative problems suggestive of marginal ulceration (*Table 2*)[22–27,29,33,40]. The incidence of this problem has ranged from zero to 19 per cent which is in the same range as has been reported for the classic pancreatoduodenectomy which includes a vagotomy Moreover, most patients with marginal ulceration after PPPD have been easily controlled with medical management.

A number of authors have studied the effects of pancreatic resection on acid and gastrin production. Traverso and Longmire[37] studied basal and stimulated acid output in eight patients at a mean of six months following PPPD. They observed low–normal basal (0–4 1 mmol/h) and stimulated (0·1–224 mmol/h) acid production. Pearlman and his associates[25] also reported similar findings. Pearlman and associates reported a variable stimulated gastrin response after PPPD but persistent hypergastrinaemia was not seen[28]. Sudo and colleagues[75] analysed gastrin production before and after a standard Whipple resection. They found that both fasting and stimulated gastrin levels were reduced following pancreatoduodenectomy. Takuda and associates[76] compared 20 patients with PPPD, 27 patients with the classic Whipple procedure, and eight healthy controls. They found that postprandial gastrin and secretin were normal after PPPD but significantly diminished after the classic Whipple. Similarly, Kim *et al*[29] found that serum gastrin and gastric acid were normal after their modification of the PPPD and decreased with the classic Whipple operation. Thus, both experimental and clinical evidence suggest that the PPPD is not an ulcerogenic procedure.

Postoperative nutrition

One of the theoretical advantages of PPPD is improved nutrition. Most patients who undergo the classic Whipple procedure are unable to achieve their preoperative weight[32]. However, Braasch and his colleagues[31,32] have documented that patients undergoing PPPD regained a median of 101 per cent of preoperative weight and 95 per cent of preillness weight Fink and his associates[40] also studied serum levels of vitamins A and B_{12}, iron, total iron-binding capacity, carotene, and folate in both PPPD and classic Whipple patients. No differences were noted between the two groups, and vitamins A, B_{12} and folate levels were normal in all patients. Of six patients undergoing PPPD, serum iron levels were low in two, total iron-binding capacity was increased in three, and serum carotene levels were low in five. However, similar abnormalities were observed in classic Whipple patients. Thus, current data suggest that weight and the majority of nutritional parameters are normal after PPPD

Conclusion

PPPD represents one of the most significant recent advances in pancreatic surgery. The operation can be performed with a very low mortality and morbidity and is technically easier than the standard Whipple resection Gastric emptying may be prolonged transiently in the immediate postoperative period. However, this complication is easily managed and is not a long-term problem. In addition, PPPD has a lower incidence of enterogastric reflux, dumping, and diarrhoea when compared with the classic Whipple procedure Clinical and experimental evidence has substantiated the hypothesis that preservation of the pylorus would reduce the incidence of marginal ulceration following pancreatectomy. Moreover, patients undergoing PPPD are more likely to regain their preoperative and preillness weight.

Pancreatoduodenectomy with preservation of the pylorus may be the procedure of choice for chronic pancreatitis involving the head of the pancreas. Initial concerns about the use of this procedure in malignant disease have not been born out, and its use should be considered for curative or palliative resections of pancreatic and periampullary malignancies. Surgery is the only method of treatment which provides the chance of cure in patients with such pancreatic and periampullary neoplasms, and may also provide the best palliation in terms of survival and quality of life. Thus, we believe that PPPD has a significant role to play in the management of patients with pancreatic and periampullary neoplasms

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Operative choledochoscopy: common bile duct exploration is incomplete without it

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This paper reviews the reported experience of operative choledochoscopy. Development of choledochoscopes to the currently available rigid and flexible instruments is described. The collected results of both rigid and flexible choledochoscopy are reported. Retained stones occurred in 97 of 2712 stone-positive explorations with the rigid choledochoscope (3·6 per cent) and in 35 of 1726 stone-positive explorations with the flexible choledochoscope (2·0 per cent). Choledochoscopy should now be a mandatory part of common bile duct exploration.

Keywords: Choledochoscopy, retained stones, exploration of common bile duct, choledocholithiasis

Development of the choledochoscope

In 1887 Thornton described two successful cases in which common bile duct stones were crushed and removed via a dilated cystic duct. He later described two other cases in which stones were removed through a choledochotomy and the lower end of the duct was inspected with a glass speculum[1]. In 1890, Courvoisier described a case in which he reoperated to retrieve a retained stone[2]. In 1923, Bakes described a speculum with a proximal mirror which used reflected light from a surgeon's headlamp[3]. It was not until the 1940s that the first rigid optical choledochoscope was developed by MacIver[4]. It was a modified cystoscope, 5 mm in diameter with a right angle 7 cm from the tip. It provided an irrigation channel and a light source. In 1953 Wildegans started to develop a choledochoscope that incorporated an optical system with a light source and an irrigation channel enclosed in a rubber sheath. He continued to develop this instrument and by 1958 it was commercially available[5]. By the 1970s the Hopkins rod lens optical system had been developed. This system was incorporated in the Karl Storz rigid choledochoscope and offered a greater depth of field and a wide angle of view with minimal distortion of the image.

The flexible choledochoscope was first described by Shore and Lippman in 1965[6]. Optical performance was not comparable with that obtained with the then available rigid choledochoscope, but it offered greater manoeuvrability and flexibility. In the 1970s Olympus introduced the CHF series of choledochoscopes with improved fibreoptics and manoeuvrability. These flexible choledochoscopes were gradually improved and modified by Ashby[1] to the present range, the CHF-20 series.

In the 1980s further advances in fibreoptics and miniaturization have led to the development of a number of flexible choledochoscopes. The range of options available with each of these newer choledochoscopes varies with the diameter of the instruments. The larger models can accommodate the optical and illumination fibre bundles, a working channel and controls for bending the tip. With smaller diameter choledochoscopes this is not possible and one or two of these facilities cannot be accommodated. Currently choledochoscopes of 0·8–2·0 mm diameter with optical and illumination channels are being used to visualize the biliary tree. These can be introduced percutaneously[7,8], via the duodenoscope working channel[9] or via the cystic duct[10,11].

The rigid choledochoscope

The rigid choledochoscope consists of a metal shaft with a proximal lens and a distal viewing limb which is angled in relation to the shaft. Angulation of the viewing limb facilitates access to the distal common bile duct (*Figure 1*). This angulation should ideally be 90° as the costal margin tends to come into contact with the main shaft during exploration of the distal duct when 120° obtuse-angled rigid choledochoscopes are used (*Figure 2*). The viewing limb should be short,

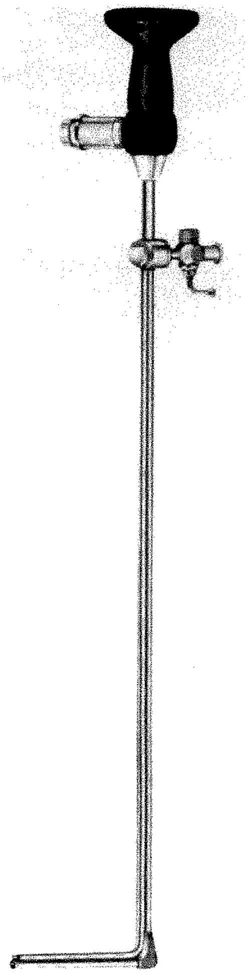

Figure 1 *The Storz rigid choledochoscope. This lightweight rigid choledochoscope incorporates the Hopkins rod lens system. The 90° shaft aids insertion into the distal common bile duct*

60–70 mm in length, to allow easy insertion into the common bile duct (*Table 1*). The Wolf choledochoscope houses an irrigation channel through which instruments can be passed while with the Storz choledochoscope the instruments are guided via a separate attachment outside the choledochoscope, which increases its working diameter.

The rigid choledochoscope is relatively cheap, robust and has excellent optical qualities due to the Hopkins rod lens system. It is probably easier to use than the flexible choledochoscope, particularly if the surgeon is unfamiliar with flexible endoscopes.

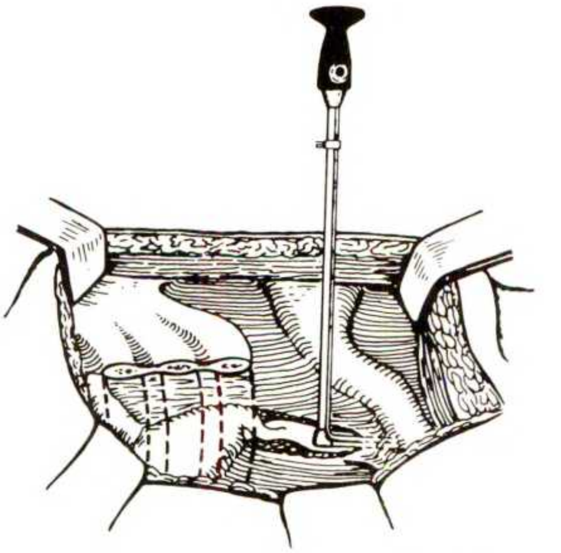

Figure 2 *The Storz rigid choledochoscope in use. The choledochotomy incision is made low down on the common bile duct just above the upper border of the duodenum. This keeps the shaft of the choledochoscope away from the costal margin. (From Motson RW, ed.* Retained Common Duct Stones – Prevention and Treatment. *London: Grune and Stratton, 1985, p 46)*

Table 1 *Rigid choledochoscopes*

Make	Model	Working length (mm)	Tip diameter (mm)	Tip angulation (°)	Field (°)	Cost* (£)
Storz	28022A	60	5·3	90	80	1195
Storz	28024A	80	5·3	90	60	1295
Wolf	8957.31	70	3·7	120	60	1519
Wolf	8958.31	70	5·9	120	60	1374

* At time of compilation; excludes value added tax

Use of peripheral attachments increases the diameter of the choledochoscope. It is sometimes difficult to visualize the extremes of the bile duct. Being a rigid instrument, it is difficult to see second or third generation intrahepatic ducts in a dilated biliary tree as the angled shaft prevents further advance of the instrument[12,13].

Occasionally adequate visualization of the papilla of Vater may be difficult, particularly when there is a long distal common bile duct ending in the distal second part or even in the third part of the duodenum. In such cases mobilization of the duodenum is essential[14]. Storz manufactures a choledochoscope with an 80 mm distal limb which can be helpful in these cases[15].

The flexible choledochoscope

This instrument has been improved considerably in recent years with advances in fibreoptics and miniaturization. The ideal choledochoscope should be light, easy to operate with one hand, have good optics and a large irrigation/working channel but have a small external diameter. In order to achieve this goal, manufacturers continue to develop their product ranges (*Table 2*).

The instrument consists of a small control unit which houses the eyepiece and a lever to control angulation of the tip. The working shaft has a length of 40 cm with graduated flexibility, being more rigid proximally to facilitate control of the tip (*Figure 3*). The tip angulation need be in only one plane as the instrument can be rotated to obtain a full range of movement. Angulation ranges to a maximum of 290°.

The diameter of the working length has decreased as

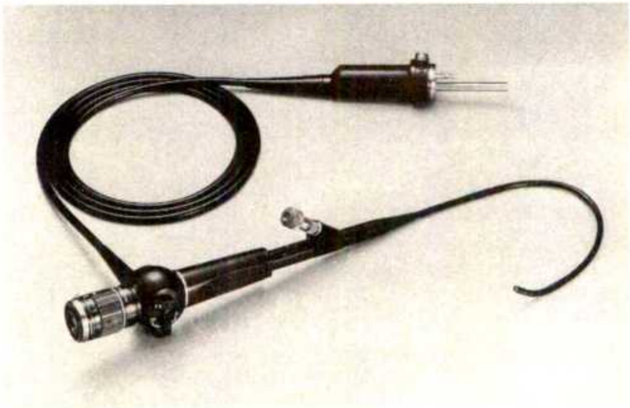

Figure 3 *The Olympus CHF-P10 flexible choledochoscope. All current flexible choledochoscopes may be sterilized by immersion. The flexible shaft makes the instrument very versatile. Instruments can be passed through the working/irrigation channel for stone retrieval under direct vision*

Table 2 *Flexible choledochoscopes*

Make	Model	Working length (mm)	Tip diameter (mm)	Channel diameter (mm)	Tip angulation (°)	Field (°)	Cost* (£)
Fujinon	CHO-SP	400	4·8	2·0	220	90	7100
Olympus	CHF-10	330	5·7	2·6	290	90	8364
Olympus	CHF-P10	330	4·8	2·0	290	90	8447
Olympus	CHF-P20	330	4·8	2·2	290	90	8810
Olympus	CHF-T20	330	6·0	2·6	230	120	8810
Storz	11001D	330	5·0	2·0	210	70	4570
Wolf-Machida	7350	400	5·0	1·6	200	60	5353
Wolf-Machida	7361	400	6·0	2·6	200	60	5353
Wolf-Machida	7370	400	7·0	2·6	200	60	5353

* At time of compilation; excludes value added tax

technology develops but the choledochoscope must house the viewing and illumination bundles, control wires, and an irrigation channel which also has to accommodate instruments for stone retrieval or biopsy forceps. These requirements will inevitably limit any substantial further reduction in diameter.

The flexible choledochoscope has increased access to the intrahepatic bile ducts and two or three subdivisions can be viewed and entered in a dilated biliary tree. Distally, the ampulla may be visualized without the mobilization of the duodenum which is often necessary when a rigid choledochoscope is used[16]. Manoeuvrability offers a great advantage during extraction of large stones. Introduction of the instrument is not impaired by the costal margin or wound edges and the cystic duct may be used as a route of entry if it is of adequate diameter[11]. Instruments pass through the irrigation channel and therefore do not increase the working diameter of the choledochoscope. Available instruments include Dormia basket, double-jointed curette, balloon catheter, quadrangular basket, grasping or biopsy forceps and irrigation catheters (*Figure 4*). Optics have improved considerably in the past few years and optical performance is now comparable to that of rigid choledochoscopes.

With the early flexible choledochoscopes sterilization by partial immersion in glutaraldehyde was necessary to avoid damage to the eyepiece which therefore remained unsterile. An alternative method which fully sterilized the instrument was the use of ethylene oxide gas sterilization, a time-consuming process lasting 24 h. All choledochoscopes of more recent manufacture are fully immersible in glutaraldehyde and can be prepared for use in 15–20 min.

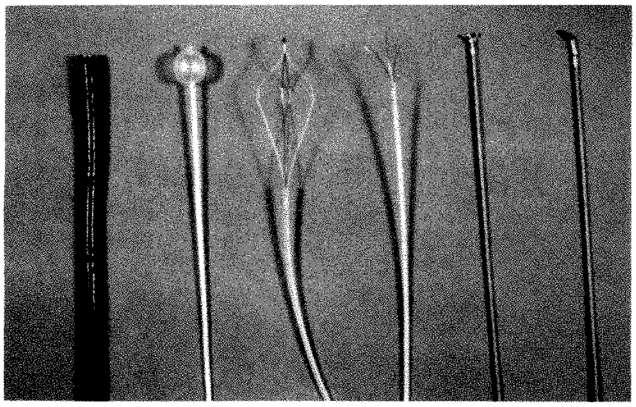

Figure 4 *Instruments for use through the channel of the flexible choledochoscope. From left to right: flexible choledochoscope for comparison, balloon catheter, quadrangular basket, quadriped forceps, biopsy forceps, double-jointed stone dislodger*

The high cost of these instruments is their principal disadvantage. They may be less robust than rigid instruments and their repair costs are higher; a major overhaul of a flexible choledochoscope equates with the purchase price of a rigid one. Choledochoscopes with an irrigation/working channel of small diameter have the disadvantage that the flow of irrigation fluid is reduced when instruments are introduced and this may restrict visualization.

Operation

The operative technique is well described elsewhere[17]. These are key points of technique which make the procedure more effective. An inferiorly placed choledochotomy incision is preferable as it may be converted into a choledochoduodenostomy if a drainage procedure is subsequently found to be necessary. Routine instrumentation of the duct is carried out with standard instruments such as Desjardins' or Randall's forceps and balloon or irrigation catheters. The choledochoscope is then used to detect additional stones and to remove any stones not retrieved by conventional exploration.

The choledochoscope is introduced into the common bile duct and the stay sutures are crossed over the choledochoscope to diminish leakage of irrigation fluid from the choledochotomy.

Systematic exploration is essential. Proximally, good views should be obtained of the right and left common hepatic ducts and, depending on the choledochoscope used, two or three main divisions of the intrahepatic ducts. This tends to be the easier part of the examination as the liver tissue supports the bile ducts. Once all visible ducts have been inspected the choledochoscope is withdrawn and reinserted into the distal common bile duct. This tends to be the more difficult part of the procedure as the duct may collapse on to the choledocoscope if the flow of saline is not adequate. The exploration should not be considered complete until the papilla of Vater is clearly visualized. Endoscopically, it has a distinctive fronded rosette appearance. If there are doubts with regard to visualization of the papilla, it can be helpful to use a Fogarty catheter which may be passed under direct vision through the papilla into the duodenum, the balloon inflated, and the 5 cm gradation mark on the catheter identified. The catheter is then slowly withdrawn, counting the marks as they pass the viewing lens into the instrument channel, until the 1 cm mark is reached (*Figure 5*). The choledochoscopist will then be viewing the papilla.

If stones are found, they may be grasped with forceps, retrieved with the Dormia basket or with the aid of a balloon catheter. If a stone is impacted or is too large for the instruments, it may be crushed with reinforced basket forceps or fragmented with ultrasound shock waves[18] or by laser[19].

After exploration of the duct with the choledochoscope, the

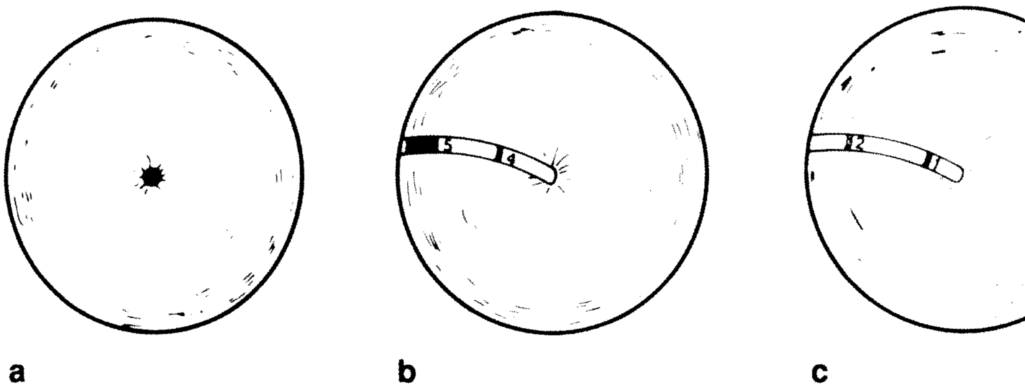

Figure 5 *Confirming the papilla has been reached. When the choledochoscopist is uncertain that the papilla has been reached when viewing the distal common bile duct* **a**, *a calibrated catheter is advanced into the duodenum* **b**. *The balloon is inflated and the catheter is then withdrawn until the 1 cm mark is in view* **c**. *This confirms that the tip of the choledochoscope has reached the papilla. (From Motson RW, ed.* Retained Common Duct Stones – Prevention and Treatment. *London: Grune and Stratton, 1985, p46)*

Table 3 *Results of rigid choledochoscopy*

Reference	Year	Stone-positive exploration	No. retained stones	Percentage of retained stones
Wildegans[5]	1958	94	1	1·1
Brocks[23]	1959	14	0	0·0
Schein[24]	1969	117	1	0·9
Leslie[25]	1974	71	0	0·0
Shore *et al.*[26]	1975	70	3	4·3
Griffin[27]	1976	25	0	0·0
Nora *et al.*[28]	1977	208	4	1·9
Fourtanier *et al.*[29]	1978	60	1	1·6
Kappas *et al.*[30]	1979	67	9	13·4
Botticher and Knoch[31]	1980	76	1	1·3
Boulenger *et al.*[32]	1979	78	1	1·3
Motson *et al.*[22]	1980	40	2	5·0
Lennert[33]	1976	148	3	2·0
Feliciano *et al.*[34]	1980	79	7	8·9
Rattner and Warshaw[35]	1981	144	6	4·2
Broadie *et al.*[36]	1981	32	2	6·3
Ernst and Windsor[37]	1982	38	1	2·7
Kappes *et al.*[38]	1982	87	2	2·3
Pot[39]	1982	200	9	4·5
Heuman *et al.*[40]	1982	73	7	9·6
Broe *et al.*[41]	1983	88	4	3·5
King and String[42]	1983	24	1	4·2
Dayton *et al.*[43]	1984	53	7	13·2
Escat *et al.*[44]	1985	303	10	3·3
Stubbs and Blumgart[45]	1984	17	1	5·8
Leahy and Peel[46]	1985	33	0	0·0
Eleftheriadis *et al.*[47]	1985	30	1	3·3
Lau *et al.*[48]	1987	23	1	4·3
Johnson and Hosking[49]	1987	68	4	5·8
Lennert[50]	1987	352	8	2·3
Total		2712	97	3·6

duct should be closed with absorbable sutures and with T tube drainage. A large (16–18 Fr) T tube should always be used. Smaller tubes have no advantages and if subsequent instrumentation of the track is necessary a large T tube avoids the need for dilatation of the track.

The alternative to choledochoscopy is peroperative, postexploratory cholangiography. It is possible to obtain good T tube cholangiograms on the table, but the process is time consuming and the choledochotomy must be reopened if stones are found. Small Foley catheters can be used for cholangiography before closure of the duct[17,20]. Either of these techniques is preferable to the omission of a postexploratory check altogether, but air bubbles and spasm of the sphincter of Oddi can sometimes make interpretation difficult[17,21].

A T tube cholangiogram should be taken on the eighth to tenth day after operation to exclude retained stones and confirm good drainage of bile into the duodenum. If retained stones are seen, the T tube should be left *in situ* to allow a fibrous track to develop which may be used for postoperative instrumentation or choledochoscopy for stone retrieval.

It is of course possible to close the common bile duct without T tube drainage, and a confident choledochoscopist may do this. However, T tubes have few complications and it is our preference to continue to use one to retain access to the duct in the unlikely event of a stone remaining, and to audit our results.

Results

In most series reviewed where choledochoscopy has been used, further stones are found within the biliary tree after conventional exploration. These stones should be regarded as additional stones found. The term retained stones should refer only to stones found on postoperative T tube cholangiography. Retained stones should be expressed as a percentage of the number of stone-positive explorations and should not be related to the total number of common bile duct explorations[17,22]. In some reports authors have incorrectly related the numbers of retained stones to the total number of choledochoscopies performed (including explorations at which no stones were found) when calculating their incidence of retained stones. This can be very misleading, particularly when there is a high negative exploration rate. The percentage incidence of retained stones in *Tables 3* and *4* has therefore been related to the number of stone-positive explorations at which the choledochoscope was used. In addition, patients in whom an internal drainage procedure, such as choledochoduodenostomy without T tube drainage, has been performed, and who therefore lack postoperative confirmation of the presence or absence of retained stones, have also been omitted. In some cases, therefore, the incidence of retained stones given in the tables is higher than quoted in the original papers.

Stones seen but left *in situ* should not be considered a failure

Table 4 *Results of flexible choledochoscopy*

Reference	Year	Stone-positive exploration	No. retained stones	Percentage of retained stones
Shore and Shore[51]	1970	100	4	4·0
Longland[52]	1975	49	2	4·1
Stotter *et al.*[53]	1975	20	0	0·0
Finnis and Rowntree[54]	1977	70	0	0·0
Legrand *et al.*[55]	1978	200	4	2·0
Yap *et al.*[56]	1980	84	4	4·8
Bauer *et al.*[57]	1981	36	1	2·8
Grange and Maillard[58]	1981	47	0	0·0
Wang[59]	1982	47	1	2·1
Chen *et al.*[60]	1983	184	2	1·1
Gartell and McGinn[61]	1984	31	1	3·2
Leggeri *et al.*[62]	1984	128	2	1·6
Ashby[63]	1984	65	1	1·5
May and Corfield[64]	1985	33	3	9·0
Eleftheriadis *et al.*[47]	1985	88	0	0·0
Ashby[65]	1985	70	1	1·4
Jakimowicz *et al.*[66]	1985	26	0	0·0
Jakimowicz *et al.*[67]	1986	238	5	2·1
Choi *et al.*[13]	1987	65	3	4·6
Markowitz *et al.*[73]	1987	102	0	0·0
Molina *et al.*[74]	1988	36	1	2·8
Total		1719	35	2·0

Table 5 *Results of conventional exploration of common bile duct*

Reference	Year	Stone-positive exploration	No. retained stones	Percentage of retained stones
Isaacs and Davies[70]	1960			5·0
Way *et al.*[71]	1972			10·0
Le Quesne *et al.*[21]	1975	78	1	1·3
Stubbs and Blumgart[45]	1984	23	3	13·0
Gartell and McGinn[61]	1984	32	6	18·7
Rogers *et al.*[72]	1985	55	7	12·7
Jakimowicz *et al.*[67]	1986	40	3	7·5
Neoptolemos *et al.*[73]	1987	59	5	8·5
Sheridan *et al.*[74]	1987	191	37	19·4
Total				10·6

of detection by choledochoscopy; such cases reflect the limitations of the techniques used to retrieve stones. They are, however, still retained stones and have been included in the tables.

Conventional common bile duct exploration without choledochoscopy

Few series are now reported on the results of exploration of the common bile duct where instrumentation alone is carried out and not followed by choledochoscopy (*Table 5*). The mean incidence of retained stones is 10·6 per cent (median 10·0 per cent). The lowest retained stone rate was 1·3 per cent in the series reported by Le Quesne's group from the Middlesex Hospital[21]. Peroperative postexploratory T tube cholangiography was used in this series which has never been updated.

Even though some authors have obtained good results after conventional exploration of the common bile duct, there has been no apparent major improvement in recent years using these techniques alone

Rigid choledochoscopy

With the use of the rigid choledochoscope, the incidence of retained stones is lower (*Table 3*) with a mean incidence of 3·6 per cent (median 3·3 per cent).

If one assumes that the population in question is similar and the only parameter that has changed is the introduction of the use of the choledochoscope, then the incidence of retained stones is significantly lower ($P<0{\cdot}001$) when the rigid choledochoscope is used compared with conventional common bile duct exploration.

Two series[30,43] with retained stones in 13 per cent of cases mar the results of rigid choledochoscopy. If these two series, which are outside the 99 per cent confidence limits of the entire group, are omitted, the mean incidence of retained stones after rigid choledochoscopy is 3·3 per cent. The apparent increase in incidence of retained stones with the rigid choledochoscope in recent years is difficult to explain. The fixed length of the viewing limb may well have resulted in some stones being missed, particularly distally in patients with a long common duct or proximally in the upper branches of the hepatic ducts.

Flexible choledochoscopy

The flexible choledochoscope offers greater versatility and manoeuvrability, allowing a more complete exploration of the duct. When the published data are analysed, the mean retained stone rate of 2·0 per cent (median 1·85 per cent) is lower than that achieved with either conventional exploration or rigid choledochoscopy (*Table 4*). Furthermore, with the increasing use of the choledochoscope, the results obtained represent a significant improvement over the rigid choledochoscope ($P = 0{\cdot}005$). If the result of May and Corfield[64], which is outside the 99 per cent confidence limit of the entire group, is excluded the mean incidence of retained stones after flexible choledochoscopy is 1·9 per cent.

The improvement of results in recent years with the flexible choledochoscope is encouraging and suggests that the problem of retained common bile duct stones could be resolved in the 1990s if the use of choledochoscopes continues to grow.

Postexploratory cholangiography is a second-best technique when compared with the direct vision of choledochoscopy. It is, however, to be preferred to no postexploratory check whatsoever. The simple method of using one or two small Foley catheters before common duct closure provides satisfactory films within the limitations of the technique[17,20]. Interpretation is really limited to defining the presence or absence of filling defects.

Complications

It is uncertain whether complications such as a bile leak from the choledochotomy, pancreatitis or wound infection are due to the use of the choledochoscope, as these complications also occur after conventional exploration. However, these complications do not seem to be more frequent when a choledochoscope is used[17,27,36,43,57]. Kappas *et al*[30] had one case of septicaemia in a patient with infected bile in whom high infusion pressures were used to clear the duct of debris before choledochoscopy. Recovery was uneventful after conservative management. Injury to the common bile duct is very rare. A single case of perforation has occurred while using an older rigid choledochoscope with a 120° rather than 90° viewing limb[22]. This was noted and repaired at the time without further complications. There have been no reports of injuries occurring with either the 90° rigid or flexible choledochoscopes There have been two reports of aspiration of infused saline from the nasopharynx when large volumes of irrigation have been used, some of which has refluxed through the pylorus[75,76]. Neither of us has encountered this problem but it is probably reasonable to insert a nasogastric tube after a prolonged choledochoscopy. The technique must now be regarded as very safe with no increase in general or specific complications.

Current practice

It is now well established that choledochoscopy reduces the incidence of retained common bile duct stones in patients with choledocholithiasis. There are no randomized controlled trials comparing choledochoscopy with postexploratory cholangiography and few surgeons who have used modern choledochoscopes would wish to take part in such a trial It should follow therefore that the technique should be widely used. Unfortunately this is not the case.

Availability of choledochoscopes in hospitals in the USA varies greatly from 29 per cent in Alabama[77] to 84 per cent in California[78]. No similar surveys have been published in the UK. Usage of the choledochoscope differs extensively in those hospitals where the instrument is available. In the Californian survey, only 8 per cent of surgeons used the choledochoscope routinely in common duct operations[78] but in an international series a much higher proportion (62 per cent) used choledochoscopy routinely[79]. In the UK, a recent survey showed that only one-third of general surgeons always use choledochoscopy after bile duct exploration and that 37 per cent never use it[80].

It is difficult to justify the poor acceptance of choledochoscopy. The cost of the instrument should not be an issue when compared with the cost of treatment of a patient with a retained stone. The operative technique has been well described and is not a difficult procedure. Models for teaching choledochoscopy techniques have also been described[81,82].

In an international survey of 1072 consecutive operations for stone-related biliary tract disorders, the incidence of retained common bile duct stones was high (4·5 per cent) and occurred almost exclusively in institutions in which intraoperative cholangiography and choledochoscopy were omitted or infrequently used[79].

Future practice

With routine use of operative choledochoscopy, it should be possible to reduce further the incidence of retained stones, thus decreasing the morbidity and mortality of bile duct surgery.

The advent of smaller endoscopes will make it possible to examine the common bile duct via the cystic duct and may displace operative cholangiography as the preferred method for determining the presence or absence of common bile duct stones. However, the lack of a 'road map' image of the biliary tree is a potential disadvantage of using small choledochoscopes as the initial exploring instrument, and their role will be determined only by carefully conducted clinical trials. Early experience with small choledochoscopes confirms that good distal views are usually obtained but that there are difficulties in angulating the choledochoscope to obtain adequate views of the hepatic ducts[83].

In a small number of patients stones detected by choledochoscopy cannot be removed with stone basket, balloons or grasping forceps (R. W. Motson, unpublished data). In such cases, the success of common duct and intrahepatic duct clearance may improve further as new techniques such as mechanical, ultrasonic[18] or laser[19] lithotripsy are perfected.

The high quality of choledochoscopes that are now available provides surgeons with the opportunity to explore the common bile duct with a degree of thoroughness that cannot be achieved by previously accepted methods of exploration. It is now possible for the retained common bile duct stone to become a rarity but this is unlikely to occur without the routine use of a choledochoscope, preferably a flexible instrument, at the time of common bile duct exploration.

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Primary hepatic malignancy: the role of liver transplantation

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Between January 1982 and April 1989, 134 patients with a suspected liver neoplasm were referred to the liver unit, Queen Elizabeth Hospital, Birmingham. In 105 (78 per cent), a primary hepatic neoplasm was histologically confirmed, and 47 patients (45 per cent) proved to have primary hepatocellular carcinoma. Twenty-nine orthotopic liver transplants were performed in 28 of these patients (27 per cent). Twenty patients (71 per cent) survived 30 days or longer (median 11·5 months; range 2–87 months), of whom nine are currently alive. We retrospectively analysed our data to determine the influence of preoperative evaluation, histological type and staging on outcome. Computed tomography proved to be superior to intraoperative assessment (86 versus 58 per cent) in diagnosing tumour positive nodes. Patients with tumour negative lymphadenopathy had a better prognosis. Postoperative stage I/II had a median survival of 16 months (range 3–87 months) compared with 7·5 months (range 2–20 months) for stage III. Non-cirrhotic patients with hepatocellular carcinoma had the best prognosis; cholangiocellular carcinoma and cirrhotic patients with hepatocellular carcinoma had the worst outcome with no survivors beyond 1 year. Because of the advanced stage of disease at the time of presentation, the value of liver transplantation in primary liver cancer is limited. For those presenting with advanced disease confined to the liver (stage I/II) in whom conventional hepatic resection is not possible, significant benefit can be achieved in selected cases.

Keywords: Primary hepatic malignancy, liver neoplasms, transplantation, assessment, outcome

Complete surgical excision represents the only chance of cure for patients with primary liver malignancy. The presence of advanced cirrhosis or multifocal hepatic malignant disease means that only a small proportion of patients will be offered an attempt at segmental resection and, of these, approximately 30 per cent will survive 5 years[1]. In 1967 in Denver, Starzl *et al.* performed the first orthotopic liver transplant (OLT) for hepatocellular carcinoma on an 18-month-old girl who survived 13 months[2] Since then, many other patients with primary hepatic malignancy have undergone total hepatectomy and liver replacement in an effort to clear all malignancy.

Disappointing results, largely due to the high incidence of tumour recurrence, led several centres to discontinue liver grafting for primary tumours[3] but some of the longest survivors have been transplanted for this indication[4–6] Because of the difficulties in assessing the extent of nodal involvement with tumour or tumour extension at the time of surgery, an approach based on detailed preoperative assessment to detect extrahepatic spread and thus stage the disease, has been advocated[5].

We have analysed our own experience and attempted to determine the accuracy of both preoperative and intraoperative assessment of disease and to correlate stage of disease with patient outcome following liver transplantation.

Patients and methods

Between January 1982 and April 1989, 134 patients with suspected liver neoplasm were referred to the Liver Unit, Queen Elizabeth Hospital, Birmingham (*Table 1*). In 105 patients a diagnosis of primary liver tumour was confirmed histologically Twenty patients of 47 with hepatocellular carcinoma were excluded from the analysis (advanced disease and not offered a transplant, died during assessment or while waiting for a liver graft) and six others had an exploratory lapararotomy (two underwent liver resection, one had a palliative biliary drainage procedure and three were inoperable). The remaining 21 patients, 15 with hepatocellular carcinoma and six patients with the fibrolamellar variety underwent OLT Transplantation was also performed in three of 42 patients (one incidental) with central cholangiocellular carcinoma and in four of 16 patients with tumours of mesenchymal origin

Primary hepatic malignancy was the main indication for liver transplantation in 22 patients Six patients had liver replacement primarily to treat end-stage cirrhotic liver disease and were found to have a coincidental tumour either before transplantation or at histological examination of the excised liver. All patients underwent preoperative assessment to detect the extent of disease[4].

A total of 29 grafts was performed in 28 patients (15 male) with a mean age 38·5 years; range 3–65 (*Table 2*). Operative technique and immunosuppression has been previously reported[4] with the exception of venovenous bypass[7], recently used in selected cases Abnormal radiological appearance of lymph nodes on preoperative scan in the

Table 1 *Histological classification of liver tumours*

Histological diagnosis	Number of patients ($n = 134$)	Number transplanted
Hepatocellular carcinoma		
Non-fibrolamellar	40	15 (53·6)
Fibrolamellar	7	6 (21·4)
Cholangiocellular carcinoma	42	3 (10·7)
Mesenchymal tumours	16	4 (14·3)
Giant cavernous haemangioma	5	
Epithelioid haemangioendothelioma	2	(1)
Infantile haemangioendothelioma	1	(1)
Angiosarcoma	5	(2)
Leiomyosarcoma	2	
Spindle cell tumour	1	
Metastatic	29	

Numbers in parentheses are percentages of the total numbers

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Table 2 *Orthotopic liver transplantation (OLT) for primary hepatic malignancy*

OLT number	Age	Sex	Tumour type	CT +ve	IO +ve	HIST +ve	Size (cm)	CE	Survival (months)	Cause of death
Cirrhotic										
1	54	F	NF HCC	n.a	Y	N	11	Y	0	Sepsis
6	55	M	NF HCC	n.a	N	N	m.f.	Y	0	Infarction
9	13	M	NF HCC	N	N	Y	m.f	N	2	Recurrence
48	59	M	NF HCC	N	Y	N	10	Y	12	Recurrence
60/62	56	M	NF HCC	N	Y	N	1	Y	0	Bleed
78	22	F	NF HCC	N	N	N	1·5	Y	0	Rejection, necrosis
79	45	M	NF HCC	N	N	N	m.f	Y	0	Bleed
117	46	M	NF HCC	N	N	N	m.f.	Y	3	Hepatitis B recurrence
119	55	M	NF HCC	N	N	N	m.f.	Y	0	MOF
126	65	M	NF HCC	N	Y	N	m.f.	Y	0	Bleed
Non-cirrhotic										
2	39	M	NF HCC	n.a.	Y	N	22	Y	87	
5	44	M	NF HCC	N	Y	Y	m.f	N	6	Recurrence
7	60	F	NF HCC	N	N	N	16	Y	71	
146	49	M	NF HCC	Y	N	N	15	Y	13	Recurrence
226	38	F	NF HCC	N	N	N	m.f	N	5	
25	21	M	FL HCC	Y	Y	Y	15	N	18	Recurrence
28	27	F	FL HCC	N	Y	Y	15	N	0	Bleed
32	19	F	FL HCC	N	Y	N	18	N	20	Recurrence
70	23	F	FL HCC	N	N	N	16	Y	34	
131	21	F	FL HCC	N	Y	N	16	Y	19	
214	18	M	FL HCC	Y	Y	Y	18	N	8	
16	47	F	EHE	N	N	N	m.f	Y	55	
39	53	F	CholCa	Y	Y	Y	m.f.	N	12	Recurrence
43	46	F	CholCa	Y	Y	Y	m.f	N	11	Recurrence
65	33	F	AS	Y	Y	Y	m.f	N	5	? recurrence
139	40	M	CholCa	Y	N	N	m.f	N	7	Recurrence
237	37	M	AS	N	N	N	m.f.	Y	4	
241	3	F	IHE	N	N	N	20	Y	4	

Three patients were node negative but had incomplete excision of tumour (OLT 32 and 226 had tumour in the portal vein, OLT 139 had tumour in the extrahepatic bile duct). OLT 60/62 had a second liver graft 1 month after the first transplant. CT/IO/HIST relate to presence (Y) or absence (N) of enlarged nodes on computed tomography (CT) and intraoperatively (IO) and to tumour positive nodes at postoperative histology (HIST). n.a., not available; m.f., multifocal; CE, complete excision; MOF, multiorgan failure, NF HCC, non-fibrolamellar hepatocellular carcinoma; FL HCC, fibrolamellar hepatocellular carcinoma; CholCa, cholangiocellular carcinoma, AS, angiosarcoma, EHE, epithelioid haemangioendothelioma; IHE, infantile haemangioendothelioma

porta hepatis and coeliac axis was not considered an absolute contraindication to transplantation. These patients were subsequently defined as computed tomography (CT) positive for the purpose of this study. Any patient with lymph nodes that appeared macroscopically 'abnormal' intraoperatively (IO) was defined as IO-positive. Microscopic tumour in one or more nodes in the resected specimen was defined as histology (HIST) positive.

Lymph node status and stage of disease (Fortner Classification[8]) were correlated with outcome. The latter is a postoperative clinicopathological staging method. In this study stage II denotes a tumour confined to the liver but not amenable to complete excision by conventional techniques. CT scan and intraoperative macroscopic findings were compared with histology for their accuracy in determining node status.

Results

Non-fibrolamellar hepatocellular carcinoma

Fifteen patients (53 per cent) had non-fibrolamellar hepatocellular carcinoma (*Table 2*). In ten patients a diagnosis of hepatocellular carcinoma was made pretransplant. Two patients with hepatitis B, cirrhosis and raised α-fetoprotein levels were suspected of harboring a tumour but neither had preoperative histological or radiological confirmation. Three patients transplanted for chronic liver disease were found to have an incidental tumour on histological examination. Three of the five patients with occult neoplasm and five out of ten patients with preoperative histological diagnosis had multifocal tumour. In the unifocal group, the size of the occult tumours was 1 and 1·5 cm and, in those with a pretransplant diagnosis of tumour, it ranged from 10 to 22 cm (mean 16 cm).

Seven (46 per cent) of these 15 patients, all with cirrhosis, died within 30 days of transplantation due to operative and postoperative bleeding (four), graft failure (two) and sepsis (one). Of the eight patients who survived the operation, three with hepatocellular carcinoma and cirrhosis (two positive for hepatitis B virus surface antigen) were dead at 1 year. One of these (OLT 117), with a raised serum α-fetoprotein level and positive for hepatitis B virus surface antigen but without preoperative histological confirmation of malignancy, had a multifocal tumour and was dead at 3 months with possible recurrence of hepatitis B infection (autopsy findings not available). Another patient (OLT 48) positive for hepatitis B virus surface antigen and with a 10 cm unifocal tumour, had complete resection but died at 12 months with bone metastases. Retransplantation was necessary in one patient (OLT 60/62; positive for hepatitis B virus surface antigen and cirrhosis) one month after the first graft because of hepatic artery thrombosis but died of perioperative bleeding.

Five patients had non-fibrolamellar hepatocellular carcinoma without associated cirrhosis. Two patients (OLT 5 and OLT 146) with a sclerosing variant of hepatocellular carcinoma associated with hypercalcaemia (4·9 and 2·8 mmol/l· normal range 2·2–2·6) and normal parathyroid hormone levels, developed hepatic recurrence with raised serum calcium levels and died at 6 and 13 months. Of the remaining three, one with multifocal tumour and incomplete excision (portal vein infiltration) is alive at 5 months and the other two (both unifocal) are alive at 71 and 87 months respectively.

Fibrolamellar hepatocellular carcinoma

Six (21 per cent) of the 28 patients transplanted had fibrolamellar hepatocellular carcinoma. The mean age of this group (four female) was 21·5 years (range 18–27 years) and tumour size ranged from 15 to 18 cm (mean 16 cm) Four had had a previous laparotomy with a view to resection that had proved possible in only one (OLT 70). One patient died after operation from bleeding.

Two died with recurrence at 18 and 20 months but both had incomplete resection, one with tumour positive nodes (OLT 25) and the other with portal vein infiltration (OLT 32). The disease free interval for the former patient was 6 months when he developed recurrence in the abdominal scar and lungs simultaneously. Despite chemotherapy he died 12 months later with tumour recurrence in the graft The latter patient had a disease free interval of 16 months, developing recurrence in the abdomen and the grafted liver and died 4 months later (without chemotherapy).

One patient, OLT 70 (extended hepatic resection, 32 months pretransplant) was disease free from 24 months following a complete excision of the tumour at transplantation but developed metastases in the chest wall and local recurrence in the graft. This patient had chemotherapy and is alive with a good quality of life at 34 months post-transplant. The other two patients (one with metastatic lymphadenopathy) are alive and disease free at 8 and 19 months.

Other tumours

All three patients with cholangiocellular carcinoma had incomplete excision with multifocal tumour on histological examination, and died within 1 year from metastatic disease. One patient (OLT 39) was a therapeutic failure (sepsis, rejection recurrence) requiring hospitalization for most of her post-transplant life (12 months). Another patient (OLT 43) who previously had had a total colectomy and ileostomy did not pose any major technical problems during the transplant operation, had a disease free survival of 10 months. In the third patient (OLT 139), transplanted for primary sclerosing cholangitis, cholangiocellular carcinoma was an incidental finding One of the two patients with angiosarcoma (OLT 65) died at 5 months with widespread intra-abdominal recurrence. The patient with epithelioid haemangioendothelioma (OLT 16; 47 years) was node negative and alive at 55 months. The 3-year-old patient (OLT 241) with infantile haemangioendothelioma was also node negative but with a 20 cm unifocal tumour and is alive and disease free at 4 months

Prognostic factors and outcome

Twenty (71 per cent) patients survived 30 days or longer (median 11·5 months, range 2–84 months), of whom nine are currently alive.

Nodal assessment. The comparison between the three methods of evaluation of node status is shown in *Table 3*. The accuracy of normal and abnormal CT scan readings was 77 per cent and 86 per cent respectively.

Table 3 *Accuracy of node status by CT scan, intraoperative assessment and histology*

	Sensitivity (per cent)	Specificity (per cent)	Positive predictive value (per cent)	Negative predictive value (per cent)
CT+ve *versus* HIST+ve	67	91	86	77
IO+ve *versus* HIST+ve	58	55	58	55

CT+ve, computed tomography scan positive; HIST+ve, histology positive, IO+ve, intraoperative assessment positive

Table 4 *Postoperative node status, Fortner stage and survival*

		Survival		
Status	Patients (n)	Median (months)	Range (months)	Number alive
Node negative	13	13	3–87	8
Node positive	7	8	2–18	1
Stage I/II	10	16	3–87	7
Stage III	10	7·5	2–20	2

Table 5 *Transplantation for primary hepatic malignancy*

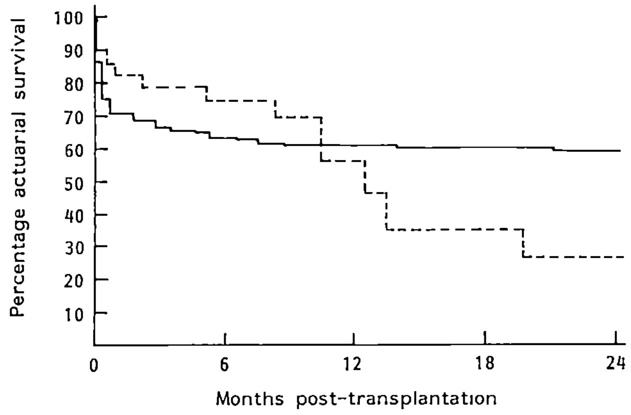
		Survival		
	Patients (n)	Median (months)	Range (months)	Number alive
Non-fibrolamellar hepatocellular carcinoma with cirrhosis	10	0	0–12	0
Non-fibrolamellar hepatocellular carcinoma without cirrhosis	5	13	5–87	3
Fibrolamellar hepatocellular carcinoma	6	18·5	0–34	3
Cholangiocarcinoma	3	11	7–12	0
Tumours of mesenchymal origin	4	15·5	3–55	3

Node status and staging Eight patients died within 30 days of surgery. These patients were excluded because death was due to perioperative complications and unrelated to node status, completeness of excision or recurrent disease (four were stage I/II and four were stage III). Thirteen patients with no histological evidence of tumour in hilar nodes (but including three with local infiltration) had a median survival of 13 months (range 3–87 months) in contrast to those with microscopic tumour in the porta hepatis and coeliac nodes who had a median survival of 8 months (range 2–18 months), with no survivors beyond 18 months. Ten patients were classified as stage I/II, and ten as stage III (including three patients who had tumour infiltration of the portal vein/extrahepatic bile duct). The different survival for each stage is shown in *Table 4*.

Histological type Cholangiocarcinoma and hepatocellular carcinoma with cirrhosis have the worst prognosis. The best outcome has been in the groups with non-fibrolamellar hepatocellular carcinoma without cirrhosis and fibrolamellar hepatocellular carcinoma (*Table 5*). The actuarial survival of patients with acute or chronic liver disease ($n=215$) and primary hepatic malignancy ($n=28$) after OLT is shown in *Figure 1*.

Discussion

The high recurrence rate, despite careful preoperative radiological and meticulous intraoperative evaluation, has led some groups to question the value of liver replacement as a curative therapy for primary liver malignancy[5]. In Europe, 635 patients have had an OLT for liver cancer, the majority for hepatocellular carcinoma (63 per cent). Three year survival rate ranges from 25 per cent for hepatocellular carcinoma to 18 per cent for secondary liver tumours[9]



Number at risk

Non-tumours	215	97	74	38
Tumours	28	13	10	4

Figure 1 *Actuarial survival of patients with acute or chronic parenchymal disease* (n=*215*, ——) *and primary hepatic malignancy* (n=*28*, ---) *after orthotopic liver transplantation*

Our data supports the concept that lymph node status is a prognostic factor in the long term survival of cancer patients following liver transplantation[10] The Hannover group[5] used a modified tumour nodes metastasis (TNM) staging system in their retrospective analysis of 95 liver recipients Node negative patients (pN_0) with hepatocellular carcinoma had a 2 year actuarial survival rate of 36 per cent compared with no survivors beyond 1 year ($P<0{\cdot}05$) in those with lymph node metastases (pN_1).

The accuracy of CT scanning to detect intrahepatic size of tumours is equivocal as reported by Mittal and colleagues[11]. There is little published data on the accuracy of CT scanning in detecting metastatic lymphadenopathy in liver cancer. Imaging techniques such as CT scanning are inaccurate in detecting lesions <1·0 cm in diameter[12] and nodes with micrometastases may not be enlarged CT scanning proved superior in sensitivity, specificity and accuracy of diagnosis compared with intraoperative findings. The accuracy of CT scanning in predicting tumour positive nodes is 86 per cent. Nevertheless, 23 per cent of patients undergoing transplantation will have tumour positive nodes despite a normal CT scan (*Table 4*). Nodes that appear abnormal to the surgeon at operation will, on histological examination, contain tumour deposits in 45 per cent of cases. Similar data on the inaccuracy of intraoperative assessment of lymph node involvement in gastric cancer has been reported[13].

It can be assumed that patients with tumour positive nodes or local infiltration have had an incomplete excision (residual tumour). This view is supported by the fact that only 50 per cent of our patients who survived 30 days or longer were classified as stage I/II with a median survival of 16 months, compared with 7·5 months in the stage III group. From this experience, it is clear that 'curative' liver transplantation for primary hepatic malignancy can only be considered when the tumour is confined to the liver (stage I and II). Nevertheless, even in node negative cases, recurrence of tumour may occur, suggesting that micrometastatic seedlings were present at the time of transplantation.

Recently, the Pittsburgh team has embarked on a more radical approach, the so called 'cluster' procedure[14] This involves *en-bloc* resection of the native liver, pancreas, duodenum, spleen, stomach, proximal jejunum and ascending and transverse colon and replacement by a composite 'cluster' consisting of liver, pancreas and duodenum removed *en-bloc* from the donor. Nine of 11 patients are alive at 1 to 6 months although the follow-up is insufficient to comment on recurrence of tumour. This procedure may reduce the incidence of residual disease and local recurrence but long-term survival data is awaited.

In this series hepatocellular carcinoma with cirrhosis carries a poor prognosis. Only one patient survived for 12 months and, despite a complete resection, he subsequently died with bone metastases. The management of a patient with cirrhosis and a small tumour is controversial. Kinami *et al.*[15] have shown a consistent correlation between tumour size in cirrhotic patients and time of recurrence after limited hepatic resection Good results have also been obtained by the Pittsburgh group[16] in patients who were transplanted for chronic liver disease and found at postoperative histology to have an incidental tumour (<5 cm); 13 of 14 patients are alive at follow-up of 3 to 73 months, six surviving beyond 3 years. The availability of intraoperative ultrasound scan[17,18] has increased the number of limited segmental resections in patients with a small tumour and cirrhosis. The choice of partial excision *versus* liver replacement should be taken in the light of age, functional hepatic reserve, dysplasia[19], portal hypertension and outcome.

The proportion of patients transplanted for the fibrolamellar tumour in this series is greater than in previous reports[5,16,20]. In this series patients with fibrolamellar hepatocellular carcinoma presented late (four of six patients in stage III). Even with incomplete resection confirmed histologically, good palliation has been achieved in three patients with metastatic disease with a mean disease free interval of 14 months, one still alive at 34 months. When comparing the fibrolamellar variant with non-fibrolamellar hepatocellular carcinoma without cirrhosis, there appear to be similarities in the clinical outcome although our numbers are small. The macroscopic features and growth characteristics of the fibrolamellar, hepatocellular carcinoma make it amenable to surgical excision Ideally, patients with this type of tumour should be referred to a centre where the techniques of extended liver resection and OLT are available.

Cholangiocellular carcinoma in our experience has a bad prognosis (all three patients died with recurrence within 12 months of transplant). All our patients were stage III, and the Hannover group have reported similarly disappointing results for stage II tumour[5].

Tumours of mesenchymal origin represent a spectrum of relatively benign to aggressive malignancy. Epithelioid haemangioendothelioma has been reported to have a relative benign course[21,22]. This cannot be supported in our series as one patient presented with widespread metastases and another (3-years-old, OLT 241, infantile variant) in whom the massive tumour was growing at an alarming rate.

It is difficult to be accurate in tumour staging with nodal status during preoperative and intraoperative evaluation. Liver transplantation in our hands and others[5] can clearly do little to help those in stage III disease with extended nodal involvement. While more radical surgical options are currently being explored, for the most part liver transplantation will be reserved for those patients with stage I and II without nodes who can expect a survival greater than 50 per cent at 2 years.

Routine staged histological assessment of porta hepatis and hepatic artery nodes should be performed at the time of hepatectomy before proceeding to grafting. The increased liver storage times now available[23], can permit liver grafting as a semi-elective procedure during 'working' hours when histopathological evaluation is more readily available. For the stage III patients, either a more radical surgical approach is needed, as is currently being explored, or a more effective combined chemotherapy schedule must be developed. In the meantime, the role of liver transplantation for hepatic malignancy will be limited.

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Case report

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Management of intrahepatic calculi in Caroli's disease by extracorporeal shock wave lithotripsy

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Caroli's disease was first described in 1958[1] and is a rare condition frequently complicated by stones of the intrahepatic ducts which can cause repeated episodes of acute cholangitis and liver abscesses. Sauerbruch and colleagues[2] showed that extracorporeal shock wave lithotripsy (ESWL) safely fragments stones in the gallbladder and the common bile duct. We report disintegration of large intrahepatic bile duct stones by ESWL in a patient suffering from Caroli's disease.

Case report

A 27-year-old Portuguese woman was admitted in 1984 for acute cholangitis. She had a history of gallstones which had been treated by cholecystectomy 5 years previously. On admission, biochemical analysis showed a rise of the serum levels of alkaline phosphatase (1300 units/l), γ-glutamyltranspeptidase (850 units/l), aminotransferases (serum glutamic oxaloacetic transaminase, SGOT, 190 units/l and serum glutamic pyruvic transaminase, SGPT, 307 units/l), and total bilirubin (109 μmol/l). Fever (39·0°C) and leucocytosis (white blood cell count 14000) were present. Blood cultures grew *Streptococcus fecalis* and *Haemophilus influenzae*. Ultrasound showed several dilated intrahepatic bile ducts containing echogenic material, mostly in the left hepatic lobe. Endoscopic retrograde cholangiography confirmed the presence of stones in the intrahepatic bile ducts. With medical treatment the condition of the patient improved and a left lobectomy was considered. At laparotomy the left hepatic lobe was found to be firm and irregular with marked fibrous changes. Stones were found in the right lobe of the liver and removed from segments 1 and 8 using a balloon catheter and choledochoscopy through a choledochotomy. The common bile duct was drained *via* a T tube. The postoperative course was uneventful. A cholangiogram was performed on the tenth postoperative day and residual stones were found in segment 1. The dissolution of the stones using CAPMUL (Pharmacie des Hôpitaux de Paris) by continuous perfusion *via* the T tube was attempted, but had to be stopped after 48 h because of biliary pain and vomiting. Liver function tests returned to normal and the patient was discharged in August 1984 after removal of the T tube.

The patient had no complaint for 21 months. Further episodes of acute cholangitis occurred in June 1986. Ultrasonography and endoscopic retrograde cholangiography showed stones in segments 1 and 7. Reoperation was performed for biliary decompression. Stones near the choledochotomy were removed but it was impossible to clear the biliary tree. Postoperative cholangiography showed some small residual stones and dissolution by oral chenodeoxycholic acid (15 mg/kg of body-weight per day) was attempted. The patient left hospital at the end of June 1986. She was readmitted in October 1987 for an episode of acute cholangitis. Radiological examination showed two large calculi (30 mm and 25 mm) in segment 1 (*Figure 1*). Extracorporeal lithotripsy, using a piezoelectric lithotriptor (EDAP LT01, EDAP International S.A., Marne-la-Vallée, France)[3] with ultrasonographic detection, was performed with the patient lying in

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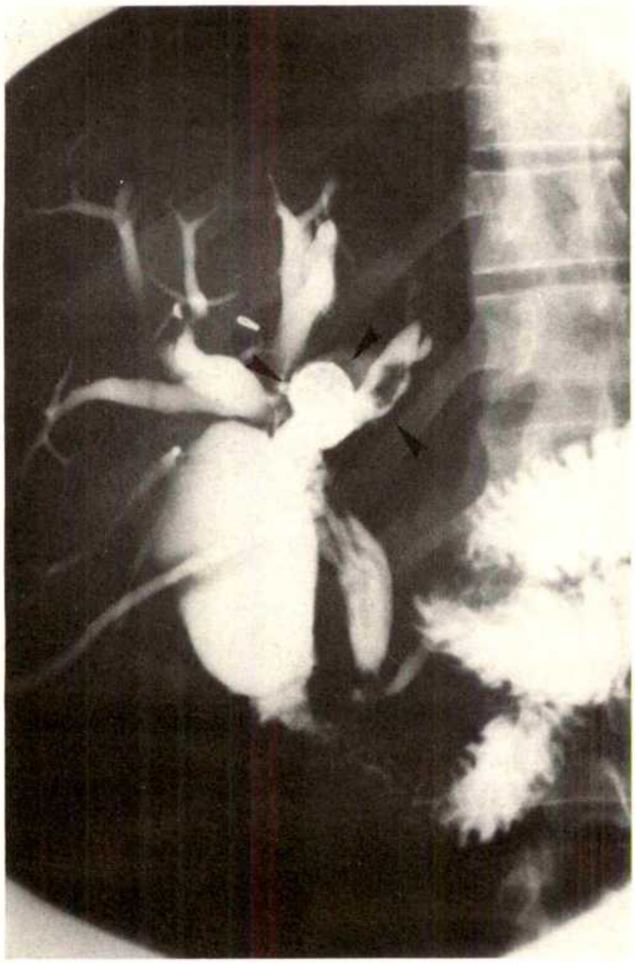

Figure 1 *Cholangiogram via a T tube. Two stones are present in the right intrahepatic duct branch (arrows) prior to lithotripsy*

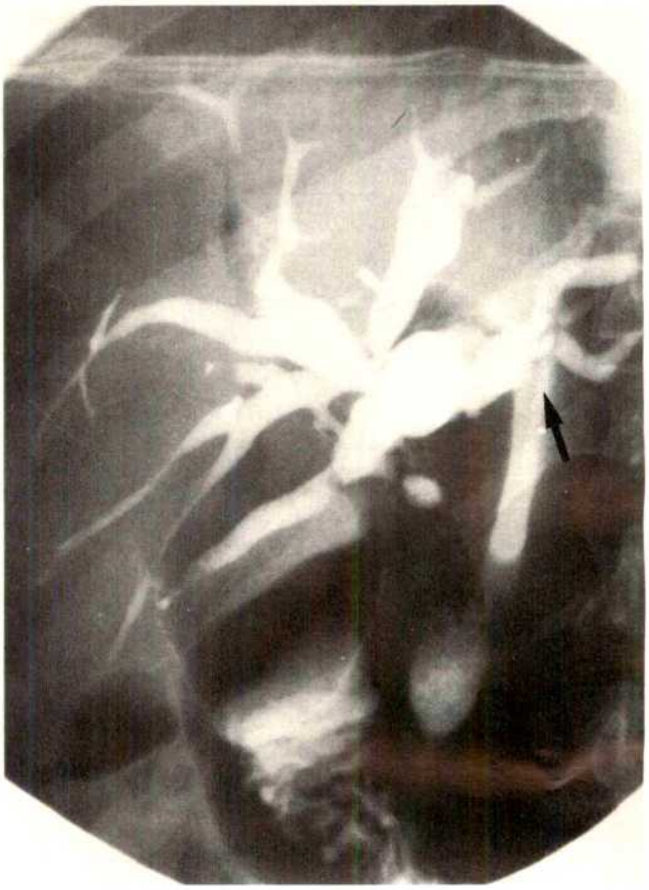

Figure 2 *Endoscpopic retrograde cholangiopancreatograph 15 days after endoscopic shock wave lithotripsy showing no residual stones present (arrowed, right hepatic duct)*

the prone position so that the shock waves entered the abdomen from the ventral side. Only one session was required. By using a period of 1 h a discharge frequency of 1·25/s for the 30-mm stone (2250 shock discharges) and a frequency of 2·50/s for the 25-mm stone (3750 shock discharges) extracorporeal lithotripsy could be performed in this patient without regional or general anaesthesia, and without premedication. Fragmentation was assessed by ultrasonography during lithotripsy and by endoscopic retrograde cholangiography 15 days after ESWL (*Figure 2*). Laboratory values showed alkaline phosphatase, 227 units/l; total bilirubin, 68 μmol/l; SGOT, 32 units/l; and SGPT, 50 units/l. The patient was subsequently seen for follow-up every 6 months, and an ERCP performed in December 1989 showed that the biliary tree was clear of calculi. At this time, the patient was free of symptoms and had had no further episode of cholangitis.

Discussion

Forms of Caroli's disease (or intrahepatic lithiasis) carry a poor prognosis, whatever the treatment. The only hope for cure lies in the discovery of an agent capable of dissolving pigment stones to avoid the infectious complications related to the presence of calculi. This case report yields important information about the treatment of intrahepatic lithiasis with ESWL for otherwise untreatable stone disease. We believe that this new modality provides a safe and effective alternative approach to the treatment of hepatolithiasis[4] in high-risk patients, such as those with Caroli's disease, avoiding the risks of both surgery and of anaesthesia.

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Mucosal intussusception to avoid ascending cholangitis

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Many methods have been devised to prevent ascending cholangitis following Kasai's hepatic portoenterostomy for biliary atresia. To investigate the effectiveness of mucosal intussusception in preventing ascending cholangitis, 20 mongrel dogs were randomized to undergo Roux-en-Y cholecystjejunostomy and common bile duct ligation with or without mucosal intussusception. Aeromonas hydrophila *was instilled into the gastrointestinal tract. Bacterial cultures were grown from samples taken from the gallbladders and lower jejunum, and blood chemistry and barium studies were performed. The barium studies showed satisfactory lack of reflux in all ten dogs with mucosal intussusception. Only two of them had positive cultures for* Aeromonas *from the gallbladder 3 days after bacterial instillation into the jejunum. All ten dogs in the control group had positive cultures for* Aeromonas *from the gallbladder. Our results showed that the mucosal intussusception group had a significantly lower rate of recovery of organisms from the gallbladder compared with the control group when the organisms were instilled into distal intestine* ($P < 0{\cdot}05$)*. The method is worthy of clinical trial as a means of preventing or treating ascending cholangitis.*

Keywords: Ascending cholangitis, portoenterostomy, mucosal intussusception, biliary atresia

Congenital biliary atresia is the most common cause of obstructive jaundice in infancy[1]. It was considered fatal until Kasai introduced hepatoportoenterostomy in 1955[2,3]. However, infection of the biliary tract is a frequent complication after this procedure and most large series of patients undergoing hepatoportoenterostomy for biliary atresia show only a 25–30 per cent survival rate[4–6]. Cholangitis has been reported in 40–60 per cent of patients with good biliary excretion[7–10]. About 80 per cent of these cases develop cholangitis within 2 months of the operation and the mortality rate due to cholangitis in these patients is as high as 25 per cent. This potentially lethal complication is often recurrent and may be resistant to antibiotic therapy[11]. Since ascending cholangitis is the most important complication in children with acceptable bile flow after operation, several investigators have modified Kasai's technique in order to avoid ascending cholangitis[12]. The present experimental study evaluates the efficacy of mucosal intussusception in preventing ascending cholangitis.

Materials and methods

Twenty mongrel dogs, weighing between 9·5 and 12 kg, were divided into two groups of ten. All animals received food and water *ad libitum*. They were fasted for 12 h before operation, and 10 mg/kg ketamine was given intramuscularly for induction. Intravenous access was then established and 25–30 mg/kg thiopentone sodium was given intravenously for maintenance. The dog was then intubated and respiration was maintained with a respirator (PMI model 101, Princeton Medical Instruments, Inc., South Natick, Massachusetts, USA). In group 1, common bile duct ligation and Roux-en-Y cholecystjejunostomy with a distance of 20 cm between the gallbladder and the enteroanastomosis and 10 cm between the jejunoduodenal flexure and the enteroanastomosis were performed through a midline incision. In group 2, a mucosal intussusception was added to the above procedure. The mucosal intussusception was made by stripping away the seromuscular layer for 6 cm in the midportion of the long limb between the gallbladder and the enteroanastomosis. The mucosa was then invaginated isoperistaltically away from the cholecystjejunostomy site to form a valve about 3 cm in length. The serosa was closed with interrupted silk sutures (*Figure 1*). Blood was drawn for total bilirubin, serum glutamic oxaloacetic transaminase (SGOT) and serum glutamic pyruvic transaminase (SGPT) concentrations before operation and 2 weeks after operation. Barium studies of the gastrointestinal tract were performed 2 weeks after operation. *Aeromonas hydrophila* was then grown on blood agar plate in an incubator at a temperature of 35°C. A solution containing *Aeromonas hydrophila* (concentration around 15×10^8/ml according to McFarland's nephelometer standards[13]) was introduced into the gastrointestinal tract of the animal through an orogastric tube after the barium studies were completed. At re-exploration 3 days later, samples from both the gallbladder and lower jejunum were taken for bacterial culture and a pressure test was conducted. The bowel distal to the mucosal intussusception site was occluded with a ribbon and a solution containing methylene blue was introduced via a polyethylene tube (internal diameter 2·5 mm, outside diameter 3·5 mm) inserted through a purse-string suture. Reflux was evidenced by identification of methylene blue in the bowel proximal to the intussuscepted mucosa. The pressure needed to cause reflux through the mucosal valve was recorded. The statistical significance of the difference in the results of culture of each group was evaluated with the χ^2 test.

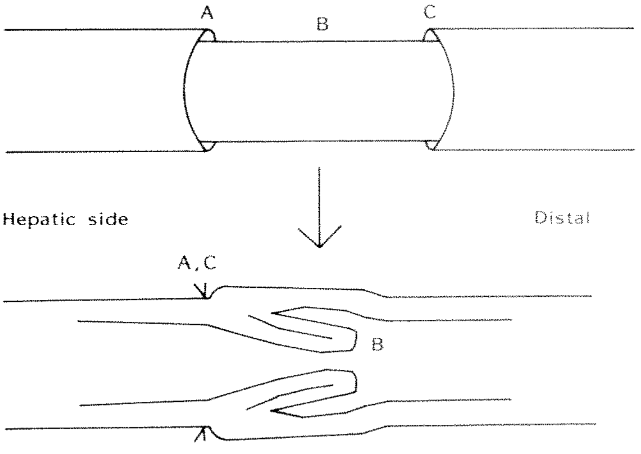

Figure 1 *Diagram of mucosal intussusception. The seromuscular layer was stripped away for 6 cm from point A to C. The midpoint B between A and C was invaginated towards the distal bowel. A was sutured to C. The seromuscular layer was then closed*

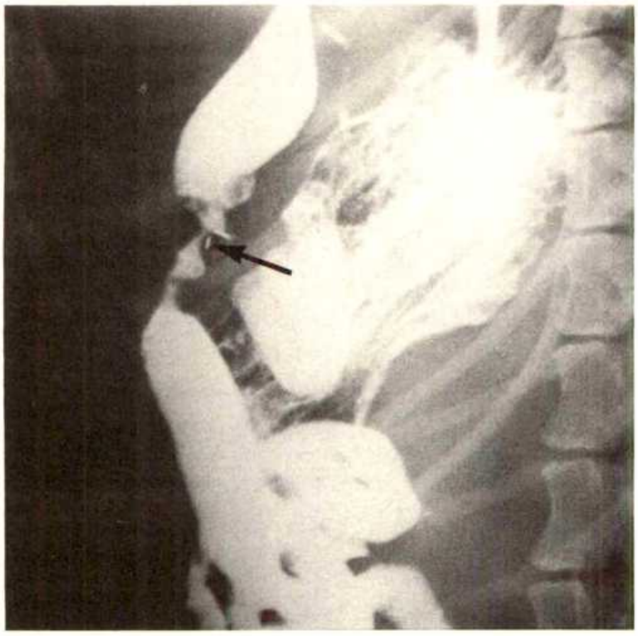

Figure 2 *Barium study of a dog in group 1 showing reflux of the contrast material up to the gallbladder. Arrow indicates metallic clip at the cholecystjejunostomy*

Results

Contrast studies of the gastrointestinal tract of all animals in group 1 showed that the contrast media could reach the gallbladder, as shown in *Figure 2*. In group 2, the contrast media could not reach the gallbladder which was marked with a metallic clip (*Figure 3*) in all ten dogs. Before operation, mean(s.d.) serum total bilirubin, SGPT and SGOT concentrations were 6·8(3·4) μmol/l, 51·3(10·8) units/l and 45·4(7·2) units/l respectively in group 1 and 6·8(3·4) μmol/l, 56·9(25·9) units/l and 51·6(12·0) units/l respectively in group 2. They were all within normal limits. After operation, the serum total bilirubin was 6·8(3·4) μmol/l in group 1 and 8·6(3·4) μmol/l in group 2. There was mild increase in SGOT and SGPT in both groups after operation (SGPT 260(156) units/l, SGOT 116(54) units/l in group 1; SGPT 344(197) units/l, SGOT 112(58) units/l in group 2). The serum bilirubin concentration in both groups remained low after operation, indicating that there was no obstruction to bile flow in all experimental animals. Diarrhoea was noted in animals having *Aeromonas* instillation. All ten dogs in group 1 had positive cultures for *Aeromonas* in both gallbladder and lower jejunum; only two dogs in group 2 had positive cultures for *Aeromonas* in gallbladders although all ten dogs in this group had positive cultures in the lower jejunum. This difference in gallbladder culture rate was significant when groups 1 and 2 were compared. After all procedures, the experimental animals were killed and there was no necrosis or obstruction at the site of mucosal intussusception. The mean(s.d.) pressure required to reflux against the valve in group 2 was 80(12) cmH_2O.

Discussion

There are three factors that may be implicated in the development of cholangitis after hepatic portoenterostomy. Cholangitis may be caused by damage to the lymph drainage system after portal area dissection[14]. The bacteria may come from either the portal system[15] or ascend directly from the intestine[8,16]. The last route of infection is favoured by the commonly employed surgical procedure in which the jejunal conduit lacks the normal choledochus sphincter action[17].

To establish a sphincter for hepatic portoenterostomy, Freud *et al.*[18] reported successful prevention of ascending cholangitis by interposing an ileocaecal segment between the porta hepatis and the jejunum. Tanaka *et al.*[19] reported only one case of ascending cholangitis in nine patients treated with 1·5 cm mucosal invagination along the long limb between the porta hepatis and the enteroanastomosis. Donahoe and Hendren[20] reported one successful case of prevention of ascending cholangitis by using a 6 cm intussusception. Moran *et al.*[21] also studied the effect of intussusception in preventing ascending cholangitis by assessing histological changes in animal experiments.

The radiological studies in our experiment showed that the intussuscepted mucosa could mechanically prevent intestinal content from ascending to the gallbladder in all group 2 animals. This is consistent with the finding that high pressures were required to produce reflux against the nipple. Kaufman *et al.*[22] reported that a 1 cm intussusception could resist a pressure of 40 cmH_2O. In our experiment, 6 cm of serosa was stripped to form a 3 cm intussuscepted valve. The mean pressure resistance in this valve was 80 cmH_2O and necrosis of the valve was not found at the end of the experiment. The blood supply to the mucosa was not compromised after separating the mucosa and the serosa along with the mesentery.

Aeromonas hydrophila are Gram-negative rod vibrios which can be isolated from water, soil and some foods. They cause haemolysis on blood agar and proliferate readily in bile. Antibiotics effective against *Aeromonas* include tetracycline, aminoglycosides and cephalosporins. The organisms are normally not present in the intestinal tract and gallbladder of dogs[23,24]. The results of our group 1 studies show that the bacteria did ascend from the jejunum to the gallbladder. The negative cultures from the gallbladders of eight dogs in group 2 prove the effectiveness of the mucosal intussusception in impeding ascent of the bacteria. Severe diarrhoea with fever was also noted in the two dogs in group 2 with positive gallbladder culture. The positive cultures might have been due to valve failure or to generalized bacteraemia. Kaufman *et al.*[22] also performed an animal study with a valved bowel loop and found no change in bacterial flora proximal to the valve when compared with control animals. Their 1 cm valve had less resistance than the 3 cm valve that we used. This may explain

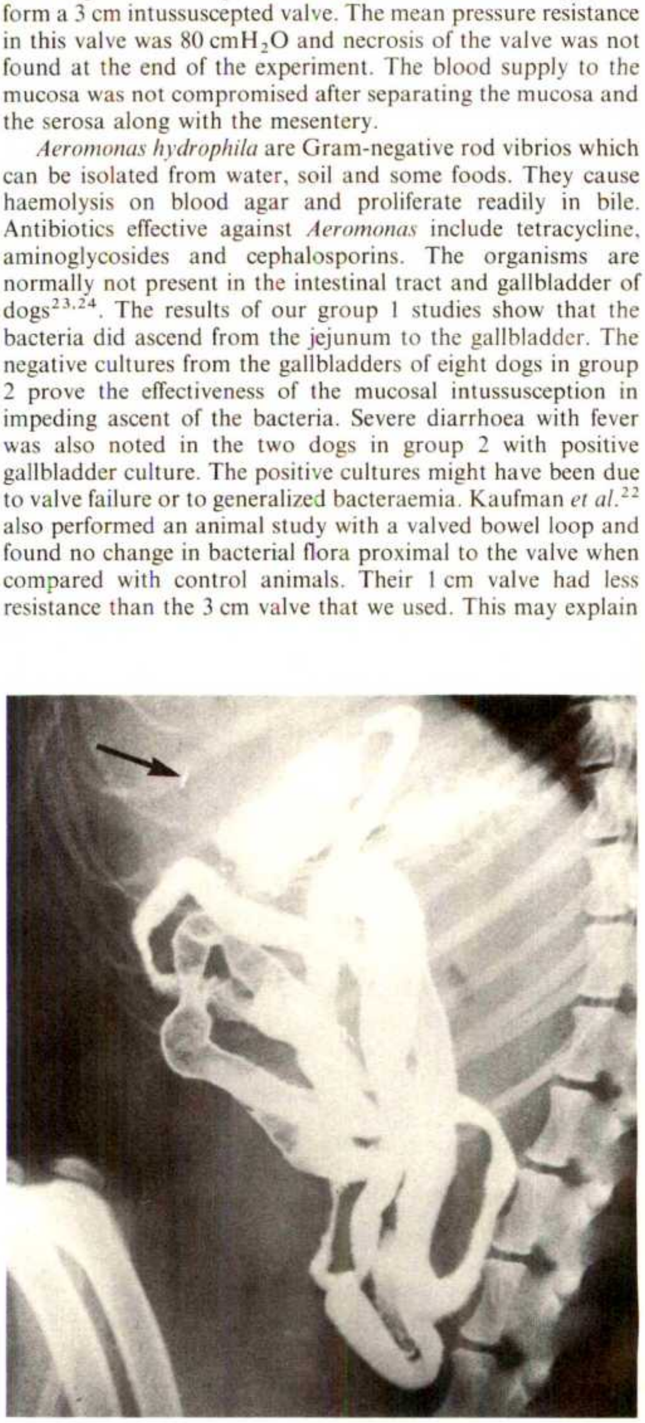

Figure 3 *Barium study of a dog in group 2 showing no reflux of contrast material up to the gallbladder. Arrow indicates metallic clip at the cholecystjejunostomy*

the difference in the results. Furthermore, bacterial culture may reveal bacterial flora already present in the proximal loop. That is why we used an organism not normally present in the intestinal tract of dogs. Our valve did not prevent contamination of the gallbladder with enteric organisms but it did prevent ascending contamination by bacteria distal to the valve.

Mucosal intussusception seems to be an acceptable method of preventing ascending cholangitis. The flow is one way and without backwash or stasis. This online one-way valve technique can be applied to all similar methods of Roux-en-Y anastomosis for biliary atresia, either as part of the primary bypass or after temporary exteriorization to document adequate bile flow. With a well functioning valve, the Roux-en-Y loop could be shorter or the anastomosis could be made directly with the duodenum instead of the jejunum. This is particularly useful for patients with a reduced length of small bowel. We believe that a clinical evaluation of this approach is worthwhile in biliary atresia and in some operations for choledochal cysts in children.

Acknowledgements

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Differing effects of pethidine and morphine on human sphincter of Oddi motility

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The aim of this study was to evaluate the effects of morphine and pethidine on human sphincter of Oddi motility. The action of these opioids on the sphincter of Oddi was evaluated by means of intraoperative manometry in 36 patients undergoing elective cholecystectomy. Both opioids were given in intravenous cumulative equipotent doses up to a maximum of 10 µg/kg morphine or 100 µg/kg pethidine. At these doses, morphine increased the mean(s.d.) frequency of contractions from 2·4(1·0) to 7·9(1·6) ($P<0{\cdot}001$)*; this effect was reduced by naloxone (0·04 mg bolus,* $P<0{\cdot}05$)*. Pethidine inhibited the frequency of contractions from 1·5(0·8) to 0·8(0·5)* ($P<0{\cdot}05$)*; this response was blocked by atropine (0·6 mg bolus,* $P<0{\cdot}01$)*. Pretreatment with atropine or naloxone reduced the frequency of contractions significantly* ($P<0{\cdot}05$)*. The results illustrate different responses to pethidine and morphine of the sphincter of Oddi, and provide a pharmacological explanation for the suitability of pethidine over morphine as the analgesic of choice in patients experiencing biliary pain.*

Keywords: Morphine, pethidine, manometry, sphincter of Oddi

Administration of morphine can cause upper abdominal pain in some patients. This pain has the characteristics of biliary colic and is thought to be due to stimulation of sphincter of Oddi motility[1]. Morphine has been shown to increase intrabiliary duct pressure[2,3] and to delay bile flow to the duodenum[4]. As a result of these effects other opioid analgesics have been used instead of morphine in the treatment of pain, including biliary pain. Pethidine is a common alternative analgesic which is used particularly in patients presenting with biliary colic.

The aim of this study was to evaluate the effects of morphine and pethidine on human sphincter of Oddi motility. A further aim was to provide an explanation for the observed different clinical responses following their administration.

Patients and methods

Sphincter of Oddi manometry was performed on 36 patients (seven men, 29 women, median age 50 years, range 19–70 years) undergoing elective cholecystectomy without evidence of common bile duct stones or anatomical abnormalities. The investigation was approved by the Committee on Clinical Investigations, Flinders Medical Centre. The patients received no opioids or anticholinergic drugs before manometry. Diazepam, 10–20 mg orally, was given as premedication. Anaesthesia was induced with thiopentone sodium 3–5 mg/kg and maintained with enflurane 1–4 per cent in nitrous oxide and oxygen (2:1). Intubation and artificial ventilation of the lungs was facilitated by vecuronium.

A triple lumen polyethylene manometry catheter of 200 cm length and with either 1·5 or 1·7 mm outer diameter was used for the manometry. The side holes in the distal end were located 2 mm apart. Each catheter lumen was infused with sterile water at a flow rate of 0·25 ml/min by a minimally compliant hydraulic capillary infusion system. The manometry was performed after completion of the operative cholangiogram and while awaiting the development of the cholangiogram radiographs. The polygraph recorder was set to zero with the catheter at the level of the common bile duct. The catheter was introduced via the cystic duct and the bile duct into the duodenum. It was then withdrawn in a stepwise fashion so that all three lumens were recording in the sphincter of Oddi[5]. The position of the catheter in the sphincter was confirmed by palpation in addition to the characteristic pressure changes seen on entering the sphincter. A minimum control activity period of 2 min was obtained before any drug was given. Drugs were then administered as intravenous bolus injections at 2 min intervals.

Patients were randomly allocated to receive one of six different regimens of drug administration. Morphine was given in cumulative doses of $2{\cdot}5+2{\cdot}5+5{\cdot}0$ µg/kg and pethidine in cumulative doses of $25+25+50$ µg/kg. Atropine was given in a bolus dose of 0·6 mg and followed by either morphine or pethidine at the above doses. Naloxone (bolus dose of 0·04 mg) was given either before or after the administration of pethidine or morphine.

Summarized, the six regimens were:

1. Three cumulative doses of morphine followed by naloxone
2. Naloxone followed by three cumulative doses of morphine
3. Atropine followed by three cumulative doses of morphine
4. Three cumulative doses of pethidine followed by naloxone
5. Naloxone followed by three cumulative doses of pethidine
6. Atropine followed by three cumulative doses of pethidine

On completion of the manometry the catheter was withdrawn and the operation proceeded as usual. It was estimated that the manometric procedure added 10–15 min to the total length of the operation. No complications could be attributed to the procedure.

Scoring and analysis of tracings

Sphincter of Oddi basal pressure, amplitude and frequency of contractions plus common bile duct pressure were scored and analysed as follows.

The basal sphincter pressure was calculated as the mean of the basal pressures above the duodenal pressure registered by the three recording channels. An increase in pressure in excess of twice basal pressure was classified as a sphincter contraction. Pressure peaks below this or with contraction rates exceeding 300 mmHg/s were considered as artefacts[6]. The amplitude of the contraction was calculated as the mean of the amplitudes above basal pressures registered in the three recording channels. The frequency of contractions was calculated over each 2 min period. The direction of propagation of the sphincter contractions was determined from the onset of the contraction in the three recording channels (*Figure 1*). Common bile duct pressure was the mean pressure recorded with the three catheter ports in the duct.

The value of the pressure profile parameters during each 2 min period were averaged. These values were used as single values for comparison between each period. All data are expressed as the mean(s.d.) unless otherwise stated.

Statistical analysis

The data were analysed using a general statistical program (Statview-512®, Brainpower Inc., Calabasas, California, USA) on a Macintosh® computer (Apple Computers Inc., Cupertino, California,

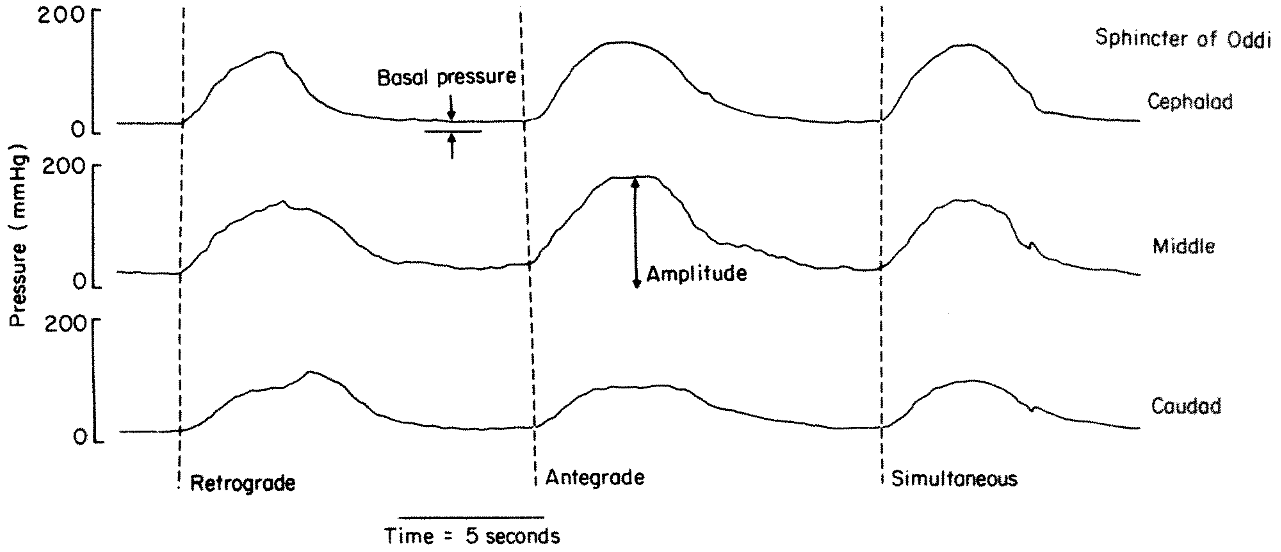

Figure 1 *Manometric recording from the sphincter of Oddi generated with a 1·5 mm outer diameter triple lumen catheter. Estimation of the basal sphincter pressure, contraction wave amplitude and direction of propagation are illustrated*

Table 1 *Pressure profile* (n = *36*)

	Mean(s.d.)
Duodenal pressure, mmHg	7·0(3·1)
Common bile duct pressure, mmHg	11·4(6·4)
Frequency of contractions, contractions/min	3·1(2·1)
Basal pressure, mmHg	17·1(9·8)
Contraction amplitude, mmHg	94·7(37·6)
Wave propagation	
Antegrade, per cent	18 (3·4)
Simultaneous, per cent	35 (5·2)
Retrograde, per cent	47 (6·0)

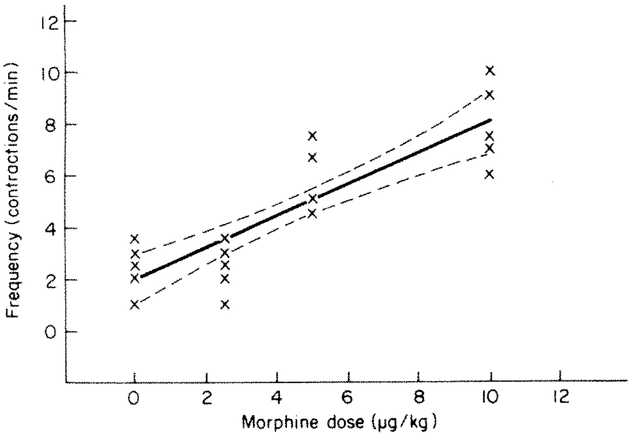

Figure 2 *The sphincter of Oddi response to cumulative doses of morphine. The frequency of contractions for each patient are plotted against the dose, and a regression line with 95 per cent confidence bands is shown. Morphine significantly increased the frequency of contractions* (P < *0·001*, n = *5*)

USA). Regression analysis was used to evaluate dose–response effects. The significance of the regression analysis was estimated using a *t*-test. A paired *t*-test was used to evaluate single dose responses and an unpaired *t*-test to compare differences between groups. A *P*-value <0·05 was considered significant.

Results

The sphincter of Oddi pressure profile for the control periods is summarized in *Table 1*. The sphincter was characterized by phasic contractions which were superimposed on a modest basal pressure. In this group of patients the majority of the phasic contractions were shown to be oriented in a retrograde direction.

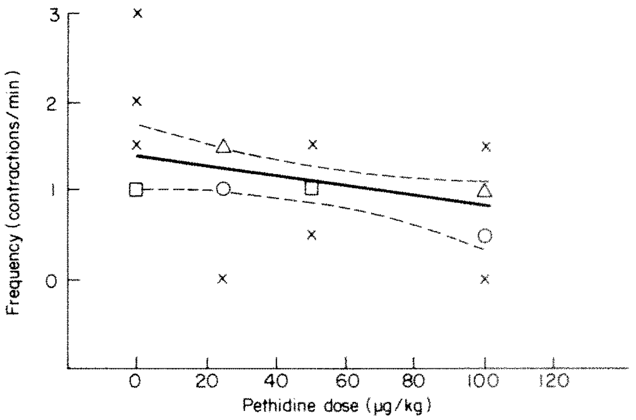

Figure 3 *The sphincter of Oddi response to cumulative doses of pethidine. The frequency of contractions for each patient is plotted against the dose* (x, *single values*), *and in the cases of overlapping values* ○ = *2*, △ = *3 and* □ = *4 values. A regression line with 95 per cent confidence bands is shown. Pethidine significantly decreased the frequency of contractions* (P < *0·05*, n = *7*)

Morphine

Following the administration of morphine, sphincter contractions demonstrated a dose-dependent increase in frequency ($P<0{\cdot}001$, $n=5$, *Figure 2*). There were no significant changes in basal sphincter pressure, contraction amplitude or wave propagation direction.

Pethidine

Administration of pethidine produced a dose-dependent decrease in the frequency of sphincter contractions ($P<0{\cdot}05$, $n=7$, *Figure 3*). There were no significant changes in basal sphincter pressure, contraction amplitude or wave propagation direction.

Atropine

Administration of atropine (0·6 mg bolus) produced a significant reduction in the sphincter contraction frequency from 3·4(2·3) to 0·8(0·7) ($P<0{\cdot}001$, $n=12$). There were no significant changes in basal sphincter pressure, contraction

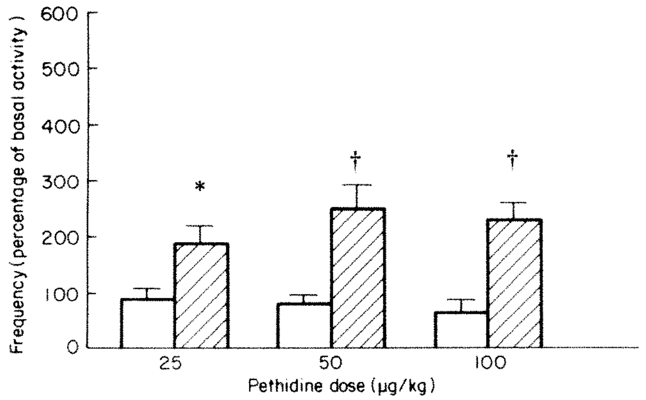

Figure 4 *The sphincter of Oddi response to cumulative doses of pethidine with (shaded bars,* n = 6*) and without (open bars,* n = 7*) pretreatment with atropine (0·6 mg bolus). The data are presented as mean with the s.e.m. indicated by the error bars.* * $P<0{\cdot}05$, † $P<0{\cdot}01$ *(unpaired* t*-test)*

amplitude or wave propagation direction. Atropine pretreatment did not alter the sphincter response to morphine ($n=6$); however, it blocked the inhibitory effect of pethidine on the sphincter ($P<0{\cdot}01$, $n=6$, *Figure 4*).

Naloxone

Administration of naloxone (0·04 mg bolus) caused a significant reduction in sphincter contraction frequency from 4·1(2·4) to 2·8(2·1) ($P<0{\cdot}05$, $n=12$). There were no significant changes in basal sphincter pressure, contraction amplitude or wave propagation direction. Naloxone pretreatment partly inhibited the effect of morphine on sphincter motility (*Figure 5*) but had no significant effect on the pethidine response. Naloxone given after the morphine reduced frequency from 7·9(1·6) to 4·6(1·9) ($P<0{\cdot}01$, $n=5$).

Discussion

Intraoperative recording of sphincter of Oddi motility demonstrates that the sphincter is characterized by phasic contractions which are superimposed on a relatively constant basal tone. Following the intravenous administration of morphine the frequency of sphincter contractions increased; however, there were no changes in the amplitude, basal pressure or wave propagation direction. This action of morphine was partly inhibited by naloxone but not by atropine. Pethidine decreased the frequency of sphincter contractions and had no effect on contraction amplitude, wave propagation direction or basal sphincter pressure. This action of pethidine was not affected by naloxone but was inhibited by atropine. These results demonstrate a difference in response of the human sphincter of Oddi to administration of approximately equipotent doses of morphine and pethidine. Morphine produces an increase in sphincter contraction frequency possibly mediated via stimulation of μ receptors, and pethidine has an inhibitory effect which is similar to that of atropine and might be produced by inhibition of endogenous excitatory cholinergic receptors. Atropine and naloxone reduced the frequency of the contractions but had no effect on amplitude, basal pressure or wave propagation direction.

Intraoperative biliary manometry uses techniques similar to those used in endoscopic sphincter manometry[7] to determine the basal sphincter pressure, frequency, amplitude and propagation of contractions. The intraoperative approach allows accurate recording of sphincter pressures without the associated technical problems of the endoscopic procedures such as patient movements and distension of the duodenum with air. Recent reports suggest that distension of the duodenum influences sphincter activity[8]. In a previous study we demonstrated that the anaesthetic effect is minimal when results are compared with those of endoscopic manometry[5]. Anaesthesia was standardized to minimize its effect on sphincter motility. The technique used provided safe anaesthesia but avoided the need to administer opioid and anticholinergic drugs before manometry.

The basal values of sphincter activity are similar to those obtained in previous studies using this method[5], as well as to those reported using endoscopic manometry[7,9]. The percentage of retrograde waves was higher when compared with healthy subjects studied by endoscopic manometry[7]. This difference may be explained by the presence of gallstones in these patients, as was demonstrated in a previous study[6].

A significant increase in the frequency of contractions of the sphincter of Oddi was seen in response to intravenous morphine injection. These results are in agreement with those reported by Helm *et al.*, who studied the sphincter response to morphine using endoscopic manometry[9]. In their study, where similar doses of morphine were given, increases in phasic wave amplitude and basal pressure in addition to frequency were demonstrated. These results are in contrast to those obtained in this study, where no significant changes in the basal pressure or amplitude of phasic contractions were recorded at these doses. The use of higher doses of morphine may produce a rise in basal pressure and wave amplitude; however, such doses were not used in our study. The effect of morphine on the sphincter contraction frequency as demonstrated by our study may result in a relative inhibition to flow through the human sphincter of Oddi and is consistent with the view that phasic sphincter contractions provide a resistance to flow through the human sphincter of Oddi[10].

Pethidine, in contrast to morphine, reduced the frequency of sphincter contractions in a dose-dependent manner. No effect on the other pressure parameters was recorded. This effect is consistent with the findings from manometry in patients with a T tube that pethidine increases biliary pressure to a lesser extent than morphine[2], and provides an explanation for the clinical view that pethidine in equipotent doses is a more appropriate analgesic for biliary colic than morphine. The types of opiate receptor that mediate the sphincter response to morphine and other opioids is not known. Morphine stimulates predominantly μ receptors[11], whereas pethidine may mediate its effect partly via other opiate receptors[12].

The sphincter of Oddi of the cat[13] and the dog[14] reacts to opioids with increased resistance to flow and, in the cat, with an increased frequency of contractions[15]. These effects are thought to be mediated by opiate receptors, which in animals are shown to exist throughout the gastrointestinal system[11]. To test this hypothesis in this study, a small dose of naloxone was given after morphine. The increase in frequency of sphincter contractions by morphine was then significantly decreased, indicating the involvement of an opiate receptor mechanism.

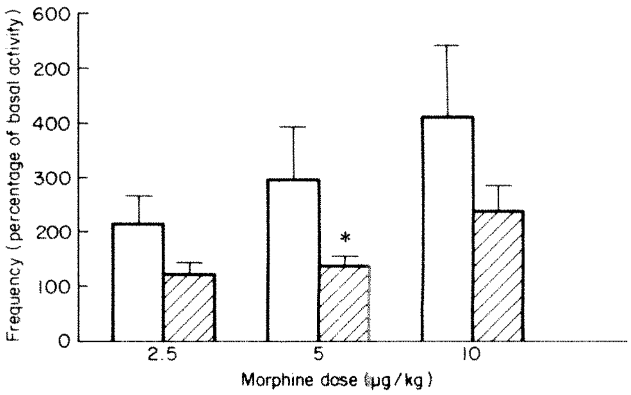

Figure 5 *Percentage changes in the frequency of sphincter of Oddi contractions induced by cumulative doses of morphine with (shaded bars,* n = 5*) and without (open bars,* n = 5*) pretreatment with naloxone (0·04 mg bolus). The data are presented as mean with the s.e.m. indicated by the error bars.* * $P<0{\cdot}05$ *(unpaired* t*-test)*

When naloxone was given before morphine a shift to the right of the dose response was evident, suggesting a competitive inhibition. Atropine decreased the frequency of sphincter contractions, indicating a basal stimulatory cholinergic influence on the sphincter, but did not prevent the increase in frequency induced by morphine. Therefore, this effect of morphine is unlikely to be mediated via a cholinergic mechanism. On the other hand, pretreatment with atropine blocked the decrease in the frequency of contractions by pethidine. This suggests that the inhibitory pethidine effect on the sphincter is mediated by cholinergic nerves. Pharmacologically, pethidine has anticholinergic effects in addition to its opiate analgesic effects[12]. As pethidine might mediate its effect partly via other opiate receptors[12], the differences observed between morphine and pethidine effects on sphincter motility in this study could also reflect different opiate receptor populations being stimulated. The ethical limitations of this study did not allow us to investigate this possibility further as this would require higher concentrations of blocking agents as well as a wider dose range of the opioids studied.

Naloxone (0·04 mg bolus) significantly decreased the sphincter contraction frequency. This effect is at variance with the observations of Helm *et al.*[9] and one study in the cat[15], but supports the results of another study in the cat sphincter of Oddi[16]. The effect of naloxone suggests an inhibition of an endogenous opiate effect on the sphincter. However, further studies in non-anaesthetized subjects are required, as an effect related to anaesthesia cannot be excluded from our study. The doses of morphine and pethidine used in this study are lower than those used clinically for pain relief; however, it is evident that at these doses the two drugs have quite different influences on the sphincter of Oddi. Pethidine, unlike morphine, did not cause a spasm of the sphincter. The tenfold difference in the administered dose of morphine and pethidine is expected to provide equipotent doses[12] and it might be expected that the distribution of the drugs would be similar[12]. To evaluate the effects by these drugs on the sphincter of Oddi in clinically used doses, steady-state levels of the drugs would need to be used, and estimations of serum concentrations would need to be performed.

The results of this study have demonstrated that the effects of morphine and pethidine on sphincter of Oddi motility are different in that morphine stimulates contractions whereas pethidine inhibits. This difference provides an explanation for the clinical observation that pethidine is the analgesic of choice in patients with biliary colic.

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Case report

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Plasma cell granuloma of the distal oesophagus

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Plasma cell granuloma is a non-neoplastic tumour composed of inflammatory cells, mainly plasma cells, within a fibrous tissue stroma. It can simulate true neoplasms, both clinically and macroscopically. For these reasons it has also been called inflammatory pseudotumour. A case of plasma cell granuloma of the distal oesophagus is described. The tumour, which was resected, showed an aggressive macroscopic appearance, with involvement of the right lung and upper stomach.

Case report

A 19-year-old woman had a 2-year history of increasing dysphagia and regurgitation, and an 8 kg weight loss. Physical examination was unremarkable, as were routine laboratory studies. Chest radiographs appeared normal. Barium swallow showed an irregular stenosis of the distal oesophagus, 5 cm in length, with suprastenotic dilatation (*Figure 1*). Endoscopy showed an oesophageal stenosis with a small, 6 mm, oesophageal ulcer of benign appearance. Biopsy did not show malignant change.

At operation through a thoracolaparotomy incision a large oesophageal mass was evident which involved the upper stomach, the hiatal ring and the middle lobe of the right lung, with adherence to the aorta, pericardium and inferior vena cava. The process was thought to be malignant in spite of non-specific changes on intraoperative biopsy of three adjacent nodes. A resection of the lower third of the oesophagus and upper third of the stomach was carried out, including the hiatal ring, and a small fragment of the middle lobe of the right lung. An intrathoracic oesophagogastric anastomosis was performed.

On the fourth postoperative day, anastomotic dehiscence was detected and the patient was subjected to thoracotomy, with suture of the anastomotic breakdown. Six days later she developed extensive pneumonia, dying 11 days after reoperation from respiratory insufficiency and sepsis without further clinical evidence of anastomotic dehiscence.

The specimen showed a diffuse infiltrative lesion of the oesophageal wall which extended to the resected fragment of the lung, and focally to the juxtacardial gastric area. The oesophageal and gastric mucosa were normal, except for a small oesophageal ulcer.

Microscopically the mass was similar throughout and consisted of fibrosis and inflammatory infiltration. Mature plasma cells constituted 95 per cent of the infiltrating cells. Russell bodies and lymphoid cells were present. There was no mitosis. The pathological diagnosis was plasma cell granuloma mainly affecting the oesophagus, but extending also to the lung, cardia and gastric wall (*Figure 2*).

Discussion

Plasma cell granuloma is a rare disease of uncertain origin, frequently described as inflammatory pseudotumour. It is composed mainly of a proliferation of polyclonal mature plasma cells within a stroma of granulation fibrous tissue. Russell bodies and spindle-shaped fibroblasts are often observed, and other inflammatory cells are usually present. Mitoses are rare. For these reasons it is considered a non-neoplastic and inflammatory process.

The condition most frequently affects the lung[1]. In a review up to 1983[2], 181 cases of lung plasma cell granuloma were collected. It is more common in young adults, and it is often asymptomatic, appearing as a solitary nodule in chest radiographs[1,2]. It is rarely diagnosed before operation, being commonly confused with carcinoma of the lung. The prognosis is generally good, although the lesion may sometimes show an aggressive course[1–5].

Inflammatory pseudotumours have been reported in several other locations such as the orbit, spinal meninges, heart, soft tissues, thyroid gland, kidney and mesothelial membranes. Within the digestive system they may occur in the liver[6–8], the spleen[9], the stomach[10–12], the abdominal cavity[13] and the oesophagus[4,14]. An alarming gross appearance has frequently been described in digestive plasma cell granulomas[6,9,11,13].

Two cases of plasma cell granuloma of the oesophagus have been recently described[14]. In addition, the oesophagus has been markedly involved in some cases of lung granuloma[1,3]. Eight of the 181 cases collected by Berardi *et al.*[2] had involvement of the mediastinum. On one occasion[4], it was not possible to be certain if the process began in the lung or in the oesophagus. In the first reported case of gastric plasma cell granuloma the lesion also affected the oesophagus[11].

Oesophageal involvement has been described as grossly localized polypoid masses[14], or as a diffuse infiltrating mass in other cases[4,11,14]. Central ulceration has been commonly found in cases of oesophageal and gastric granulomas[10–12,14].

Our patient is very similar to those reported by others[4,11,14]; the patients were young (12–33 years), their chief complaint was long-standing dysphagia and all had a locally invasive tumour that was considered to be malignant.

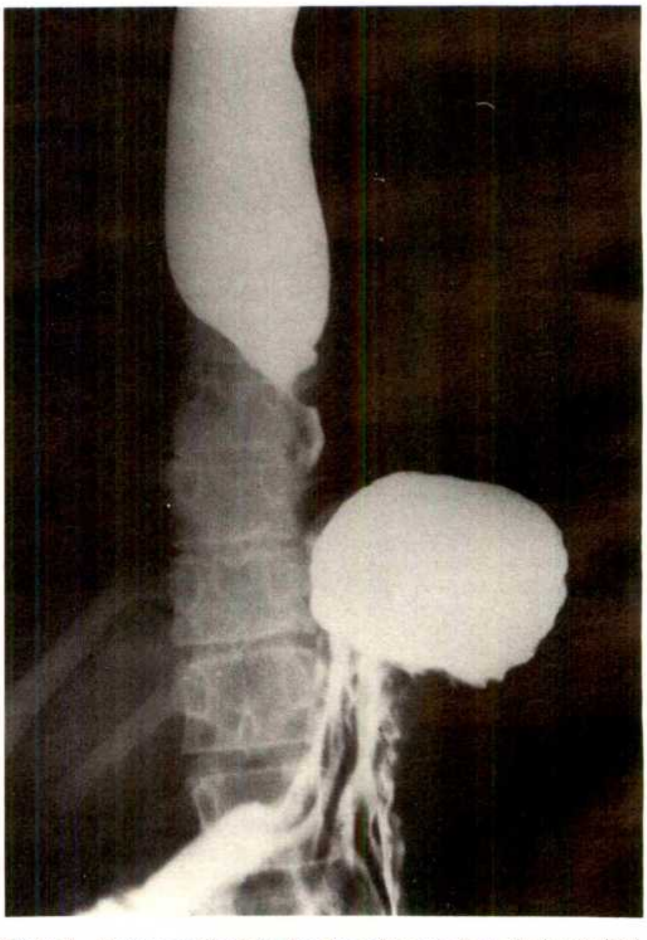

Figure 1 *Barium swallow showing irregular stenosis in the lower third of the oesophagus*

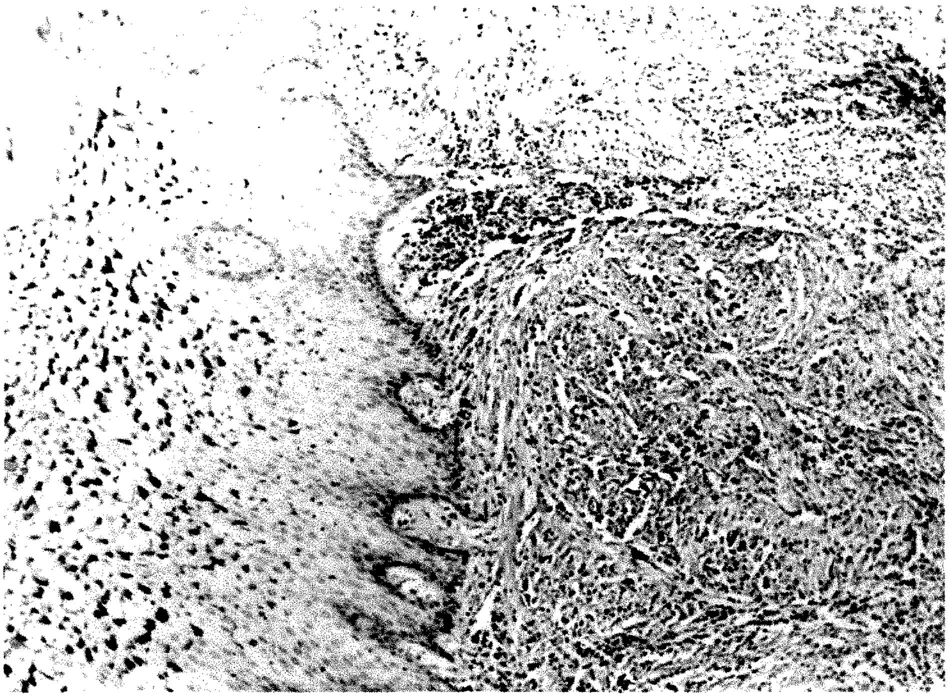

Figure 2 *Oesophageal wall with diffuse submucous inflammatory infiltration and fibrosis (haematoxylin and eosin, original magnification × 25)*

Since the preoperative diagnosis of plasma cell granuloma is difficult, operation is indicated. Complete resection of the mass, whenever possible, is the treatment of choice because if resection is not complete the tumour may recur[1,3]. Patients with oesophageal lesions have been subjected to exploratory thoracotomy[4], total gastrectomy[11], segmental resection or oesophagogastrectomy[14] (as performed in our patient).

The prognosis of lung plasma cell granuloma is generally good[1,2]. However, it may slowly grow in some cases[2], and it has an aggressive course and a worse prognosis when the mediastinum becomes involved[1–4]. Spontaneous resolution has been described in granulomas of the lung, and has also been documented in inflammatory pseudotumour of the liver[6,7].

Micro-organisms have never been found in plasma cell granulomas[2,8]. The lesion may represent a non-specific inflammatory response to a variety of agents, such as previous infection[7,8] or parenchymal necrosis[9]. It has been suggested that gastro-oesophageal plasma cell granulomas may occur as a reaction to a mucosal ulceration[13]. However, the ulcer may also be a secondary phenomenon, rather than the stimulus to formation of the granuloma[4].

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Intraoperative ultrasonography and the detection of liver metastases in patients with colorectal cancer

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A total of 213 patients with carcinoma of the colon and rectum were examined to detect liver metastases. The study compared preoperative ultrasonography and inspection and palpation of the liver during surgery with intraoperative ultrasonography. Preoperative ultrasonography, inspection and palpation identified 238 metastases in 42 patients. Intraoperative ultrasonography detected 116 previously unrecognized metastatic tumours during 40 surgical procedures ($P<0{\cdot}01$). *High resolution intraoperative ultrasonography is safe and more accurate than preoperative imaging and surgical exploratory methods. The examination is simple to perform and success appears to be related to careful attention to detail.*

Keywords: Intraoperative ultrasonography, liver metastases

Approximately 15–20 per cent of patients with carcinoma of the colon and rectum have liver metastases at the time of initial surgery, verified by preoperative ultrasonography, inspection and palpation[1–3]. Preoperative ultrasonography of the liver seems to be as accurate as computed tomographic scanning[4].

In a prospective study we have compared the accuracy of intraoperative, high resolution, real-time ultrasonography with preoperative ultrasonography and inspection and palpation during surgery.

Patients and methods

In all, 213 patients (129 men) were admitted for elective surgery for colorectal cancer between February 1987 and February 1989. The ages of the patients ranged from 27 to 84 years with an average age of 62 years. Preoperative ultrasound scanning was performed by radiologists on all patients with an Acuson 128 (Acuson Corporation, Mountain View, California, USA) ultrasonograph. During surgery, the liver was inspected and palpated. Intraoperative ultrasound examination of the liver was carried out immediately after laparotomy and before the procedure to treat the colorectal cancer. This examination was done with a real-time scanner (Brüel and Kjaer, Naerum, Denmark, type 1846) with a 7 MHz fingertip transducer.

A systematic examination of the liver was performed in both sagittal planes and by rotating movements of the transducer. The examination was performed on the superior and inferior surface of the liver.

To prevent direct contact between the sterile transducer and the liver surface, a 0·9 per cent solution of sodium chloride was used in the abdominal cavity. The biopsy procedure, accomplished by fine-needle aspiration or by Tru-Cut® (Travenol Laboratories Incorporated, Deerfield, Illinois, USA) needle, was used when a clear diagnosis of a liver lesion could not be made clinically.

Selective hepatic artery angiography was not used for diagnosing metastatic lesions, but for delineating vascular anomalies before hepatic surgery.

Results

In 150 of the 213 cases (70·4 per cent) we were not able to identify metastatic lesions either by preoperative ultrasonography or by inspection and palpation at laparotomy or by intraoperative ultrasonography. In the remaining 63 patients (29·6 per cent) a total of 354 metastatic lesions were diagnosed. In 42 patients (19·7 per cent) 238 metastatic tumours were found by routine work-up (including preoperative ultrasonography, inspection and palpation during surgery). Using intraoperative ultrasonography 57 additional metastatic lesions were found in 19 of these patients.

In 21 patients preoperative ultrasonography, inspection and palpation during surgery failed to detect small metastatic tumours. In these patients 59 tumours were diagnosed by intraoperative ultrasonography (0·3–3·5 cm in size situated 0·5–7·0 cm below the surface of the liver).

The sensitivity of the intraoperative assessment, compared with preoperative ultrasonography combined with inspection and palpation during surgery, is shown in *Table 1*. Tumours were proved by biopsy, histological assessment of resected material or subsequent growth of lesions on follow-up by ultrasonography.

Discussion

The value of intraoprative ultrasonography has already been established[5,6]. In the liver, intraoperative ultrasonography is used primarily to localize abscesses or tumours deep in the parenchyma which are not visible or palpable. Intraoperative ultrasonography is essential for some types of liver surgery, e.g. hepatic resection for hepatocellular carcinoma[7–14]. Most metastatic hepatic tumours from colorectal cancer display characteristic features on intraoperative ultrasonographic imaging[9]. They demonstrate hyperechogenicity with a surrounding hypoechoic halo or 'bull's eye' (in our study 84 per cent of the lesions) (*Figure 1*), or a hypoechoic lesion in relation to the normal liver parenchyma (*Figure 2*). Metastatic tumours from other parts of the gut may also have the appearance of a bull's eye. Hyperechoic and hypoechoic lesions in the same liver at the same time were not seen. In one patient in our study we found three hyperechoic lesions in the right lobe and one hypoechoic tumour in the left lobe, all histologically verified.

This examination technique seems to be of value but several

Table 1 *Sensitivity of detecting hepatic metastatic tumours*

Procedure	No. of tumours detected ($n=360$)	Percentage
Preoperative ultrasonography combined with inspection and palpation during surgery	238	66·1
Intraoperative ultrasonography	354	98·3

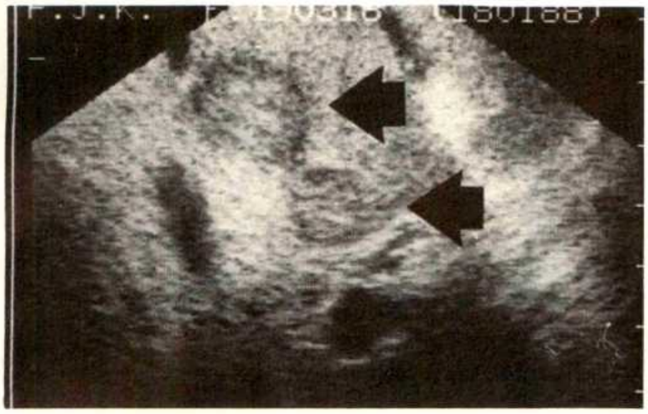

Figure 1 *Two 'bull's eye'-like hepatic metastases (black arrows) from a colon carcinoma*

authors emphasize the importance of contact between the probe and the liver[7,9,11,14]. Our experience, however, is that the slightest contact leads to a compression of the superficial 1–1·5 cm of hepatic parenchyma with subsequent loss of view of a great part of the liver. We use a solution of 0·9 per cent sodium chloride in the abdominal cavity to avoid contact between the transducer and the liver. In five patients by this means nine invisible, impalpable, lesions were discovered in the superficial hepatic area. In 40 patients (18·8 per cent) high resolution intraoperative ultrasonography identified a total of 116 histologically proven liver metastases that were unrecognized by preoperative ultrasonography and inspection and palpation of the liver. The tumours were all less than 3·5 cm in size. All but nine tumours smaller than 0·9 cm in size were situated more than 3 cm beneath the surface of the liver.

Liver metastases occur in approximately 15–20 per cent of patients following curative surgery for colorectal cancer[15,16]. In these patients metastatic tumours have been excluded by standard imaging and laboratory studies and surgical exploration. These recurrent tumours may have been present but not detected at the initial surgery because of their small size.

In this study, there were 360 identified hepatic metastases in 63 patients. The lesions were confirmed to be metastatic by resection, biopsy or continued growth on follow-up ultrasonography. There was a low sensitivity for preoperative ultrasonography and inspection and palpation at surgery. Intraoperative ultrasonography did prove to be the most sensitive indicator of the number and location of metastatic liver tumours (*Table 1*).

By exploiting all the possibilities of the instrument we were able to identify lesions smaller than 0·5 cm in size which are difficult to detect by palpation.

We advocate taking advantage of every laparotomy (i.e. gastrointestinal cancer, gallbladder surgery, etc.) to carry out ultrasonographic examination. Detailed information regarding metastases and hepatic anatomy is provided by intraoperative ultrasonography. Exact location, size and depth below the liver surface can be determined. Hepatic resection is based on the internal structure of the liver as described by Couinaud[17,18]. It is essential to define the borders between the different segments to carry out effective resections. During resection, the transducer can be used to control the direction of the resection. If hepatic surgery is not performed, ultrasonographic information may be of value for appropriate postoperative management.

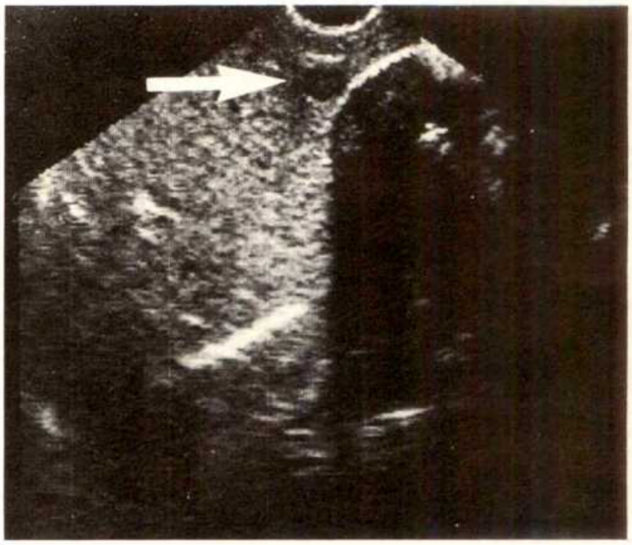

Figure 2 *Hypoechoic hepatic metastatic tumour from a rectal carcinoma (white arrow). The tumour is located in segment IV above the gallbladder*

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Papillary cystic neoplasm of the pancreas: radiological and pathological characteristics in 11 cases

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Clinical charts, radiological features, macroscopic and microscopic findings, and clinical follow-up data were retrospectively reviewed in 11 patients with papillary cystic neoplasm of the pancreas (PCNP). The patients were nine women and two men, aged from 13 to 51 years with a mean age of 25 years. The greatest diameter of the PCNPs ranged from 2·5 cm to 14·0 cm with a mean size of 7·5 cm. Six tumours were located in the tail of the pancreas, two in the body and three in the head. Most patients complained of abdominal pain or a mass. Ultrasonographic and/or computed tomography findings showed five solid, four mixed (solid and cystic) and two cystic types of tumour. Angiographically, PCNP was either a hypovascular or mild hypervascular mass with a displacement of the surrounding vessels. No vascular encasement was seen. Macroscopically all 11 tumours consisted of a well defined solid mass with degenerative change of various widths, including haemorrhage, necrosis or dystrophic calcification, and were represented by three radiological types of PCNP. The 11 patients with PCNP survived for from 3 to 253 months after curative resection without any signs of local recurrence or remote metastasis. PCNP usually affects the distal portion of the pancreas of young women. Despite its huge size, PCNP should be explored with aggressive surgical intent because of the inherently good prognosis.

Keywords: Papillary cystic neoplasm of the pancreas, ultrasonography, computed tomography, angiography

In 1959, Frantz[1] reported 'papillary tumor of the pancreas, benign or malignant?' which corresponds to the currently named papillary cystic neoplasm of the pancreas (PCNP). PCNP has been reported under various names including carcinoma of the pancreas, infantile type, adenocarcinoma of the pancreas in childhood, papillary epithelial neoplasm, solid and papillary epithelial neoplasm[2], and solid and cystic acinar cell tumour[3]. PCNP is a rare pancreatic tumour usually affecting the distal portion of the pancreas in young women[4–6]. Only a few papers have been based on a large number of cases and present findings obtained by modern diagnostic imaging techniques. We previously reported an immunohistochemical and ultrastructural study of 14 cases of PCNP[6]. In this study, we report the clinicopathological and radiological findings of 11 patients with PCNP.

Patients and methods

The 11 patients with PCNP (*Table 1*) were collected from seven institutions. Of 43 consecutive patients with pancreatic neoplasm treated in the Department of Surgery, Chihaya Hospital, between 1978 and 1987, one was diagnosed as having a PCNP, an incidence of 2 per cent. Of 46 consecutive patients with pancreatic tumour who had undergone resection in the First Department of Surgery, Faculty of Medicine, Kyushu University, between 1976 and 1989, two were found to have a PCNP, an incidence of 4 per cent. Clinical charts, macroscopy of central cut-sections, and histopathological sections stained with haematoxylin and eosin were available for all 11 patients, abdominal radiographs for 11, upper gastrointestinal radiography series for ten, ultrasonography findings for ten computed tomography (CT) scans for eight, endoscopic retrograde cholangiopancreatography (ERCP) for five and angiography for eight. A needle biopsy was performed before operation through an ultrasonographically guided puncture in one case (case 2) and during operation in another case (case 8). The biopsy specimens stained by the Papanicolaou method and Giemsa procedure were reviewed in these two cases. Eight patients with PCNP in the body or the tail of the pancreas underwent a distal pancreatectomy; one patient with PCNP in the head of the pancreas underwent pancreaticoduodenectomy; and two further patients with PCNP in the head had a complete resection of the tumour. One patient (case 5) was diagnosed as having familial adenomatosis coli (Gardner's syndrome). Clinical follow-up has been updated to 30 September 1989 and the follow-up information was obtainable for all 11 patients.

Results

Clinical findings

The 11 patients with PCNP were aged from 13 to 51 years with a mean age of 25 years. There were nine women and two men. Seven patients complained of abdominal pain, three of abdominal mass and one patient was incidentally detected as having a pancreatic tumour while hospitalized with hepatitis. Six tumours were located in the tail of the pancreas, two in the body and three in the head. The greatest diameter of the 11 tumours ranged from 2·5 to 14 cm with a mean of 7·5 cm. In seven patients, serum carcinoembryonic antigen and α-fetoprotein levels were measured before operation; no elevation was observed. No patient was diabetic. Patients with PCNP survived for from 3 to 253 months after curative resection, and distant metastasis or local recurrence was not recognized at follow-up.

Radiological findings

A diffusely calcified mass was seen in the upper abdomen on abdominal radiography of two patients (*Figure 1*) and amorphous calcification was seen in one. Upper gastrointestinal radiography series showed deformity of the stomach in six

Table 1 *Clinical findings in 11 patients with papillary cystic neoplasm of the pancreas*

Case no.	Age (years)	Sex	Chief complaint	Site of origin	Greatest diameter (cm)	Duration of follow-up (months)	Outcome
1	27	M	Hepatitis	Body	2·5	3	Alive
2*	14	F	Abdominal pain	Body	4	33	Alive
3	47	F	Abdominal pain	Tail	4	91	Alive
4	51	F	Abdominal pain	Tail	5	13	Alive
5	14	F	Abdominal pain	Head	5	106	Alive
6	17	F	Abdominal pain	Head	8	46	Alive
7	16	F	Abdominal pain	Tail	8	134	Alive
8*	21	F	Abdominal mass	Head	9	61	Alive
9	34	M	Abdominal mass	Tail	11	253	Alive
10	21	F	Abdominal pain	Tail	12	48	Alive
11	13	F	Abdominal mass	Tail	14	122	Alive

* Needle biopsy specimen was available

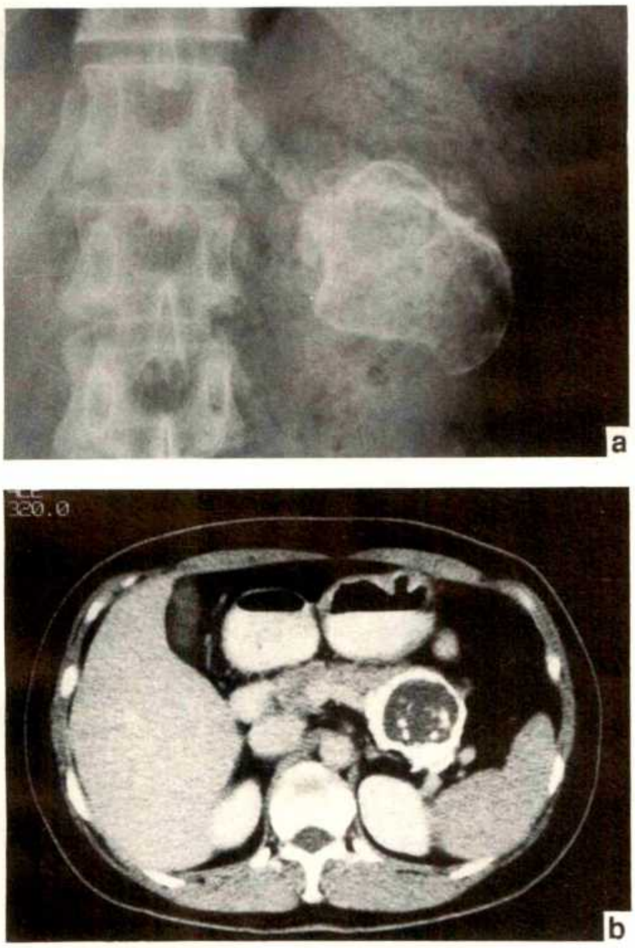

Figure 1 *Cystic type of papillary cystic neoplasm of the pancreas.* **a** *A diffusely calcified mass in the left upper quadrant (abdominal radiograph);* **b** *a calcified cystic mass (enhanced computed tomography)*

patients and enlargement of the duodenal loop in two. On endoscopic retrograde pancreatography, displacement of the main pancreatic duct was seen in three cases (*Figure 2*) and disruption of the main pancreatic duct in one. On ultrasonography and/or computed tomography (CT) scan, the tumours were of three types: solid (five cases) (*Figure 3*), mixed (solid and cystic) (four cases) (*Figure 4*) and cystic (two cases) (*Figure 1*). Ultrasonographically, the tumours were well defined, hypoechoic, solid masses in five cases, a solid mass containing cystic areas in three, a cystic mass in one and a

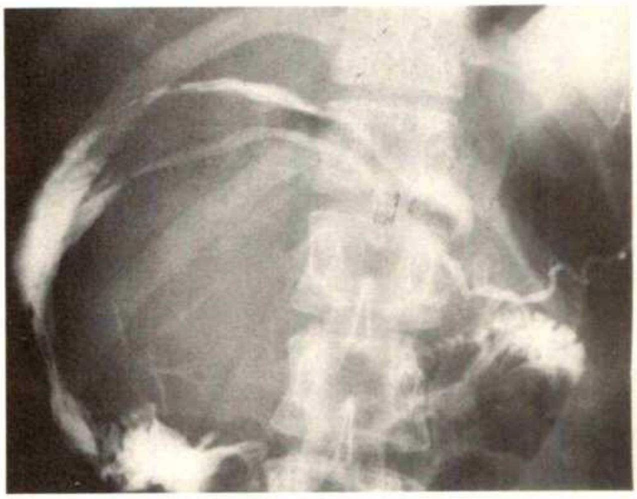

Figure 2 *Displacement of the main pancreatic duct by a huge pancreatic head mass, seen by endoscopic retrograde cholangiopancreatography*

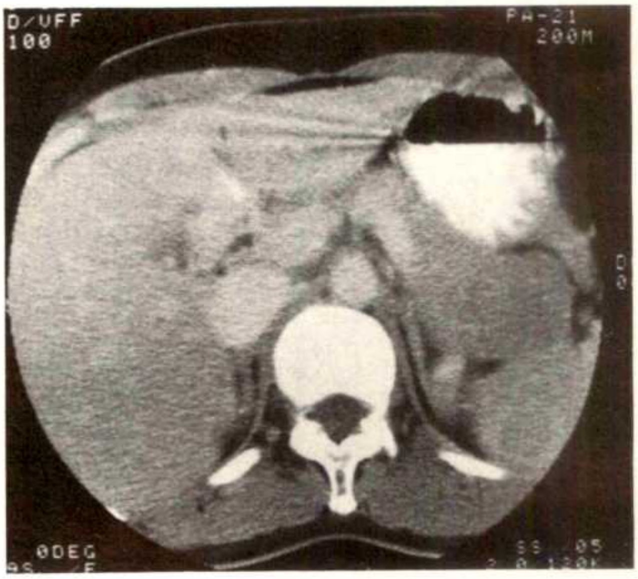

Figure 3 *Solid type of papillary cystic neoplasm of the pancreas; a low density mass in the tail of the pancreas can be seen by computed tomography*

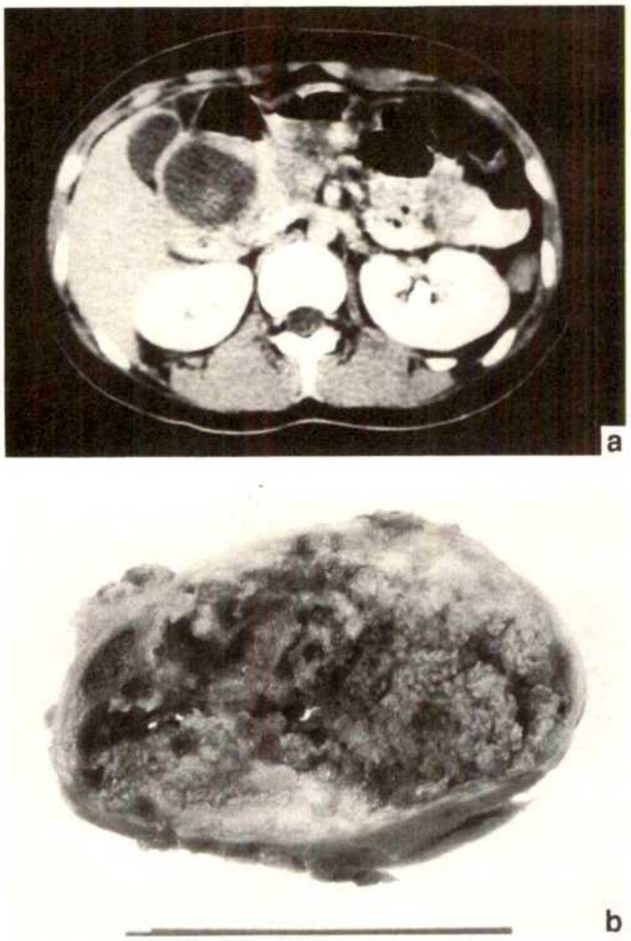

Figure 4 *Mixed type of papillary cystic neoplasm of the pancreas.* **a** *A solid and cystic mass in the head of the pancreas seen on computed tomography scan;* **b** *a solid and cystic mass*

semicircularly calcified lesion in one. On CT, the PCNP was seen as a sharply margined, low density mass in four cases, as a cystic mass in two, as a huge mass with a cystic component in one, and as a calcified cystic mass in one. In a 51-year-old woman with PCNP, a CT scan taken 5 years before the curative resection was reviewed, and the tumour was found to have remained unchanged in size and shape over the 5-year period. In eight cases examined angiographically, the tumour was found to be avascular in one, hypovascular in five, mildly hypervascular with tumour staining in one, and normal in one. No encasement of the vessels was seen but displacement and/or compression of the surrounding vessels was seen in six cases.

Pathological findings

Macroscopically, all the tumours were well defined masses with varying degrees of degenerative processes, i.e. necrosis, haemorrhage, dystrophic calcification, and cyst formation. Microscopically, the tumour had fibrous capsules in eight cases and had extended directly into the surrounding pancreas in three cases. In the tumour tissue, atypical cells were embedded in fibrous capsule showing capsular invasion of the tumour cells (*Figure 5*). The tumour cells were polygonal with clear or eosinophilic cytoplasm and centrally placed, round nuclei. Mitotic figures could be scarcely seen. The tumour cells proliferated in a solid or pseudopapillary fashion, these components gradually merging into each other. Centrally the tumour showed transformation of the solid growth pattern into pseudopapillary structures composed of pseudostratified cells over a fibrovascular stroma. Many red blood cells were seen among the papillary structures. Cholesterol clefts with foreign body giant cell reactions were occasionally seen in the stroma. In two cases, the tumour was almost totally necrotic, ghost cells formed papillary structures implying PCNP, and peripherally viable tumour cells were seen.

Two needle biopsy specimens showed a papillary structure composed of a fibrovascular core overlaid by several layers of atypical cells in a background of haemorrhage. Nests or dissociated polygonal tumour cells were present, often forming acinar structures. These cells had large, round to oval nuclei with smooth, fine granular chromatin, one or two nucleoli, and a sparse to broad cytoplasm stained green by the Papanicolaou procedure. Mitosis was rarely seen.

Radiological and pathological comparison

The well defined border of PCNP on CT and/or ultrasonography corresponded to the fibrous capsules or expansive growth of the tumour seen macroscopically. Solid areas on CT and/or ultrasonography corresponded to either the solid growth or pseudopapillary growth of the tumour cells, and the cystic portion corresponded to cystic spaces among pseudopapillary structures. Calcification on CT and/or ultrasonography corresponded to either the dense dystrophic calcification or bone formation with marrow. Mild hypervascularity of PCNP on angiography corresponded to either the vessels in the stroma or the fibrous capsules.

Discussion

PCNP is a rare exocrine pancreatic neoplasm[7–10] and about 100 cases have been reported. Morohoshi *et al.*[11] reported seven cases (2·7 per cent) of PCNP in 264 exocrine pancreatic tumours. Cubilla and Fitzgerald[12] reported one case (0·2 per cent) of PCNP in 645 malignant neoplasms of the non-endocrine pancreas. The largest single reported series was published by Compagno *et al.*[2] in 1979, in which 52 cases were described. The present small collective series of a rare PCNP is composed of 11 cases whose radiological and pathological findings are available.

The most noteworthy observation in this study was the diffusely calcified PCNP seen in two cases. Hertzanu *et al.*[13] reported two cases of unusual pancreatic calcified masses. One was PCNP and the other was a calcified pancreatic fibroma. PCNP is a low-grade malignancy and remains local for a long time, with degenerative changes.

Ultrasonography and/or CT of PCNP reveals a solid, mixed, or cystic mass[14–18], and in most cases PCNP is located in either the body or the tail of the pancreas. Ultrasonography is poor at detecting such masses, and when the tumour is calcified or cystic it is unable to show the internal structure. CT detects the internal structure and is useful in determining the organ of

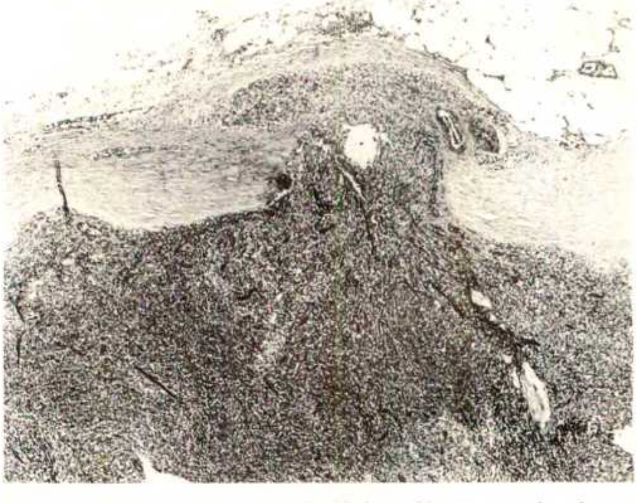

Figure 5 *Tumour cells are embedded in fibrous capsule, showing capsular invasion (haematoxylin and eosin stain; original magnification ×36)*

origin, even when the mass is huge. Ultrasonography is of more value as a screening method, whereas CT has more diagnostic value. Angiography is not of diagnostic value but is important for clarifying the vascular arrangement of the tumour, which helps to determine operability.

Preoperative percutaneous needle biopsy of the pancreas is now being safely performed. Biopsy and aspiration of cystic contents are useful in preoperative diagnosis and may influence subsequent management. In this series two patients had a needle biopsy which characteristically revealed papillary structures with a fibrovascular core overlaid by pseudostratified atypical epithelium. These features may be diagnostic of PCNP.

PCNP was divided into solid, mixed, and cystic types on ultrasonography and/or CT. In solid-type PCNP, islet cell tumours or solid pancreatic tumours should be carefully differentiated from PCNP. In the mixed type, mucinous cystic neoplasm of the pancreas[19], serous cystadenoma[19], cystic lymphangioma and cystic change of islet cell tumour should be placed in a differential diagnosis of PCNP. In the cystic type, pseudocyst, cystic change of exocrine pancreatic cancer[20] and pancreatic cyst caused by pancreatic carcinoma are to be differentiated from PCNP. An exact discrimination may be difficult.

In this study, all of the 11 patients with PCNP survived for from 3 to 253 months after curative resection without any signs of local recurrence or remote metastasis. A few cases of rare local recurrence or remote metastasis of resected PCNP have been reported[2,5,21,22]. After a complete resection of PCNP, patients should be followed clinically.

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Choice of emergency operative procedure for bleeding duodenal ulcer

In a consecutive series of 201 emergency operations in patients with bleeding duodenal ulcer the size of the ulcer was the only factor that showed a significant correlation with the procedure chosen. Vagotomy, pyloroplasty and underrunning of the bleeding point was performed in 101 cases with ten deaths (10 per cent), partial (Billroth II) gastrectomy in 81 cases with ten deaths (12 per cent), and vagotomy and antrectomy in 16 cases with one death (6 per cent). A patient was more likely to be treated by partial gastrectomy if a giant ulcer with an internal diameter of ⩾2 cm was found. The results suggest that while vagotomy and pyloroplasty, combined with a direct attack on the bleeding point or excision of an anterior ulcer is an acceptable standard emergency operation for bleeding duodenal ulcer, gastric resection proved to be a satisfactory alternative procedure and should be considered in the technically difficult case with a very large ulcer. A giant ulcer was present in 37 per cent of cases coming to surgery.

Keywords: Gastrointestinal haemorrhage, giant duodenal ulcer, vagotomy, partial gastrectomy

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In a retrospective study of bleeding duodenal ulcer in 1970, Schiller *et al.*[1] showed a steady increase over a 15-year period in the number of cases treated by truncal vagotomy, pyloroplasty and direct attack on the bleeding point (V and P). Partial (Billroth II) gastrectomy was the preferred procedure until that time[2,3]. Better results were reported with the more conservative operation, especially in older patients. They and others suggested that V and P should be the emergency procedure of choice[4–6]. While V and P may have advantages in the poor risk case, it often appears to be a less suitable choice than resection for technical reasons, especially when gross duodenal deformity and a very large or giant ulcer is found[7,8]. Pyloroplasty can be hazardous and lead to inadequate drainage in cases of giant duodenal ulcers with a diameter of 2 cm or more[9,10]. In the present study of a consecutive series of patients having emergency surgery for bleeding duodenal ulcer, a number of factors which may have influenced the surgeon in his choice of operation were examined.

Patients and methods

The clinical and operative details of 201 emergency operative procedures were studied from a consecutive series of 592 patients with bleeding duodenal ulcer admitted to one hospital from 1973 to 1987. Patients were grouped according to the type of operation performed. Risk factors and other findings in the two main groups (patients undergoing V and P and those having partial gastrectomy) were compared No patients subjected to elective surgery, including those operated upon during the index admission for bleeding, were included in the study. All patients were admitted into a specialized unit for the management of gastrointestinal bleeding[11] According to the unit protocol the indications for emergency operations for chronic peptic ulcer were: (1) exsanguinating haemorrhage; (2) shock (blood pressure <100 mmHg) within 12 h of admission in patients over 50 years of age but responding to resuscitation (operation being performed as soon as shock was brought under control), (3) further bleeding while in hospital. Policy further recommended that V and P be the standard emergency operative procedure but consultant surgeons were free to choose an alternative according to circumstance Early in the series vagotomy and antrectomy was performed in some younger patients

All but 14 operations were undertaken by consultant staff on call The 14 operations mentioned were undertaken by registrars assisted in all cases by the consultant on call.

The historical details noted were an ulcer history of greater than 3 months, previous upper gastrointestinal haemorrhage, associated medical illness American Society of Anaesthetists (ASA) rating of $\geqslant 3$ (range 1–5)[12], alcohol consumption (a recent alcohol bout or an estimated chronic consumption of more than 70 g/day) and salicylate ingestion (medication containing salicylates taken within 48 h of haemorrhage). The patient details noted included age, sex, shock within 12 h of admission (blood pressure <100 mmHg), haemoglobin on admission, endoscopic stigmata of haemorrhage (active bleeding or visible vessel), ulcer size (divided into those <2 cm or $\geqslant$2 cm in diameter as seen at endoscopy and/or at operation), units of blood transfused before surgery and whether operation was performed within 24 h of admission.

The statistical method used to compare numerical variables was the χ^2 test where appropriate

Results

There were 21 operative deaths after 201 emergency operations for bleeding duodenal ulcer. The operative rate each year was constant throughout the period of study. V and P was performed in 101 cases, standard and partial (Billroth II) gastrectomy in 81 cases, total vagotomy and antrectomy in 16 cases and other procedures in three patients. There was no significant difference in the operative mortality of 10 per cent after V and P and 12 per cent after partial gastrectomy. Early in the series 16 patients underwent vagotomy and antrectomy with gastrojejunal anastomosis, with one death. More patients suffered recurrent gastrointestinal bleeding after V and P than after resection, but the difference was not statistically significant (*Table 1*). Of the 17 patients who bled after V and P, reoperation was necessary in seven cases. Of the eight patients who bled after partial gastrectomy, one required a second operation. In this case gastrostomy and direct ligation of an anastomotic bleeding point controlled the bleeding There was no difference in the mortality rate associated with rebleeding after each procedure. One patient rebled and subsequently died after vagotomy and antrectomy. All ten cases with an anterior bleeding ulcer treated by ulcer excision, as part of the

Table 1 *Mortality and rebleeding rate after emergency surgery for bleeding duodenal ulcer*

	Truncal vagotomy pyloroplasty and direct attack on bleeding point	Partial gastrectomy
Number	101	81
Deaths	10 (10)	10 (12)
Early rebleed	17 (17)	8 (10)
Death from rebleeding*	3	2

Values in parentheses are percentages; * deaths from rebleeding are included in the total number of deaths numbered above

Table 2 *Comparison of historical details*

	Truncal vagotomy pyloroplasty and direct attack on bleeding point	Partial gastrectomy
Ulcer history of more than 3 months	55 (55)	40 (49)
Previous upper gastrointestinal haemorrhage	17 (17)	13 (16)
Associated medical illness*	67 (67)	47 (58)
Alcohol consumption	34 (34)	34 (42)
Salicylate ingestion	42 (42)	40 (49)

Values in parentheses are percentages; * American Association of Anaesthetists rating ≥ 3

Table 3 *Comparison of patient details*

	Truncal vagotomy pyloroplasty and direct attack on bleeding point ($n=101$)	Partial gastrectomy ($n=81$)
Mean age (range) in years	59·5 (18–89)	59·1 (21–83)
Males	79 (78)	57 (70)
Shock within 12 h of admission	40 (40)	23 (28)
Mean haemoglobin on admission (g/dl)	9·7	9·6
Endoscopic stigmata of haemorrhage	56 (55)	40 (49)
Large ulcer (≥ 2 cm)	22 (22)*	45 (55)
Mean preoperative units transfused	5·6	5·1
Operations performed within 24 h of admission	61 (61)	56 (70)

Values in parentheses are percentages unless otherwise stated; * $P<0\cdot01$

pyloroplasty, made an uncomplicated recovery. Early in the series, the bleeding point was not underrun in eight cases with no active bleeding at the time of surgery. Four of these (50 per cent) rebled in hospital.

Comparison of the 101 patients subjected to V and P with the 81 subjected to partial gastrectomy showed that partial gastrectomy was chosen significantly more often than V and P if the ulcer was judged to be at or greater than 2 cm in diameter ($P<0\cdot01$) (*Tables 2* and *3*). Of those patients who were shocked on admission a greater proportion were treated by V and P than by partial gastrectomy, but this difference did not reach statistical significance ($P=0\cdot1$). In 67 cases (37 per cent) the ulcer was judged at surgery to be at or greater than 2 cm in diameter. No significant difference was found between the groups in terms of other measured parameters.

Discussion

The present study shows that in the emergency surgical treatment of bleeding duodenal ulcer, partial gastrectomy was preferred to V and P in more than one-third of cases. The choice of resection was determined to a large extent by anatomical and pathological considerations, in particular the size of the ulcer. Giant ulcers with a diameter of 2 cm or more were the source of bleeding in 37 per cent of cases so the need to consider resection was relatively common. This type of ulcer merits special consideration for it is more frequently complicated by bleeding, prone to rebleed under medical management, and is associated with a mortality rate greater than that associated with complicated smaller ulcers[9,10,13].

Most studies have shown that emergency partial gastrectomy is associated with a higher operative mortality rate than V and P for bleeding duodenal ulcer[1,8,9]. This advantage of V and P is not supported by the present study, suggesting that resection is an acceptable alternative to the more conservative operation in certain cases In our study it is likely that the surgeon was able to select resection on pathological grounds because the patients were in a relatively fit state, a state that is best achieved by taking the high risk case with circulatory failure to theatre at a time determined by the patient's circulatory response to resuscitation[14,15] The protocol used required that operation was started as soon as shock was brought under control rather than the usual practice of waiting until there was evidence of further bleeding. The traditional 'wait and see' approach inevitably leads to delayed surgery and undue pressure to take the more conservative option in order to complete the operation as quickly as possible. This policy may well have been a factor behind the relatively low mortality rate of 10–12 per cent for both procedures when compared with that of 20 per cent recently reported after emergency surgery for bleeding duodenal ulcer[16]. It is nevertheless difficult to set hard and fast rules as to the best procedure for each individual case. Personal experience in dealing with the difficult duodenal stump and factors such as chronicity and severity of the ulceration must be weighed against the chance of rebleeding after V and P and the need for a second operation. If the duodenum is grossly deformed with posterosuperior scarring and stenosis, oedema and fixation, then resection and closure of the duodenum is usually necessary.

The increased rate of rebleeding after V and P compared with partial gastrectomy was not associated with an increased mortality rate from this complication. The rebleeding rate in those few patients in whom no local measures were taken to control bleeding supports the view that this strategy is inappropriate even if there is no sign of active bleeding at the time of surgery. Intermittent bleeding is a typical finding in patients who eventually die from fatal continuing arterial haemorrhage[17]. Anterior ulcers can also bleed profusely enough for surgery to be necessary even though a large artery is not involved, unlike the situation which pertains with an ulcer sited posteriorly in the duodenum. In the ten cases with anterior ulcers, excision of the ulcer as part of the pyloroplasty was successful in all cases.

The number of patients undergoing vagotomy and antrectomy in the present study was too small for further analysis. However, no advantage could be seen in the emergency situation over the two alternative procedures, V and P and partial gastrectomy. For this reason they became the only procedures performed during the latter part of the study.

Vagotomy and drainage with local measures to control bleeding, whether or not the ulcer is seen to be bleeding at the time of surgery, is probably the operation of choice for most cases of bleeding duodenal ulcer requiring emergency surgery. Partial gastrectomy is an acceptable alternative, particularly for giant ulcers in circumstances where resuscitation is ideal.

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Short note

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Laparoscopic treatment of perforated peptic ulcer

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It is accepted that emergency treatment of perforated peptic ulcer is based on surgery, namely simple closure or more definitive ulcer surgery. Occasionally, conservative treatment has been used in selected patients. The preliminary results of laparoscopic treatment of five patients with peptic ulcer perforation are reported here.

Patients and methods

Five patients, three men and two women (mean age, 46 years, range 35–79 years), had laparoscopic treatment of perforated peptic ulcer in 1989. Two patients had a previous history of peptic ulcer disease and three were taking anti-inflammatory medication

Four patients had 'a rigid board-like' abdomen on examination while the fifth had epigastric tenderness Pneumoperitoneum on plain abdominal radiography was present in all cases Perforation had occurred from 20 to 120 min after the last meal. The interval from perforation to laparoscopy ranged from 10 to 24 h

Laparoscopy was performed under general anaesthesia with induction of further pneumoperitoneum in four patients. A laparoscope was inserted at the level of the umbilicus. All patients were found to have general peritonitis At first, cleansing of the entire peritoneal cavity was performed with the help of an 'irrigation–aspiration' cannula inserted through a second incision

In four patients, the perforation was identified during laparoscopy (three duodenal, one gastric), while in the fifth patient gastroscopy on the sixth day after laparoscopy found the gastric ulcer responsible for the perforation In three instances, fibrin sealant and an omental patch were used to seal the perforation In the fourth case, a large 1 5 cm antral perforation was found, because of its size the perforation was converted into a gastrostomy by inserting a Foley catheter In three patients, abdominal drainage was instituted Finally, in all patients a nasogastric tube was positioned under laparoscopic control and aspirated half-hourly All patients received intravenous antibiotics, parenteral nutrition and ranitidine or cimetidine.

Results

In four patients the postoperative course was uneventful with commencement of bowel movements on the second or third postoperative day; parenteral nutrition was discontinued between the fifth and seventh postoperative day and the duration of hospitalization ranged from 6 to 10 days. Three of these four patients underwent endoscopy before discharge from hospital and were found to have a sealed ulcer.

The postoperative course was complicated in the fifth patient. This patient was an alcoholic and a smoker and was undergoing radiotherapy and chemotherapy for laryngeal cancer. He was also taking aspirin (6 g/day) and methyl prednisolone (120 mg/day) and his large gastric perforation was converted into a gastrostomy. Because of septic shock, laparotomy was undertaken on the seventh postoperative day but no further procedure was deemed necessary. He died 2 months later from the effects of progressive laryngeal cancer.

Discussion

A laparoscopic approach to perforated peptic ulcer has numerous potential advantages. Conservative treatment alone[1–6] or peritoneal dialysis[7], are contraindicated following perforation on a full stomach[1,2], perforation of a chronic peptic ulcer[4–6] or of a gastric ulcer[1,4,7], in elderly patients[3–5] and in patients seen late after the perforation[1,4,5]. Such patients may be treated more effectively by a laparoscopic approach. Moreover, erroneous diagnosis of peptic ulcer perforation is a disadvantage of non-operative management and may occur in 8–10 per cent of cases[3–5]; laparoscopy overcomes this diagnostic problem in most cases. Finally, it may be possible at laparoscopy to seal the perforation and to clean the abdominal cavity and it is noteworthy that intra-abdominal abscess is reported in 2–15 per cent of cases treated conservatively. With the exception of patients with associated bleeding or stenosis who require surgery, most patients may be treated by laparoscopy, whereas conservative treatment is possible in only 60–85 per cent of patients and is fully realized in 40–70 per cent of these[1–5]

When compared with surgical treatment, laparoscopy avoids wound complications and may allow easier and more comprehensive cleansing of the entire peritoneal cavity. Moreover, the absence of postoperative adhesions may allow for easier definitive surgical treatment if this becomes necessary.

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Anterior lesser curve seromyotomy and posterior truncal vagotomy *versus* truncal vagotomy and pyloroplasty in the treatment of chronic duodenal ulcer

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In a prospective randomized controlled clinical trial, anterior lesser curve seromyotomy with posterior truncal vagotomy (AMPT, $n=77$*) has been compared with truncal vagotomy and pyloroplasty (TVP,* $n=69$*) in 146 patients with chronic duodenal ulcer with a mean duration of symptoms of 7 years. The mean follow-up time was 4·5 years with a range of 2–7 years. One elderly patient died from a myocardial infarction in the TVP group. Acid secretory inhibition in response to insulin and pentagastrin stimuli was equal in both groups, indicating a similar degree of vagal denervation. Recurrent ulcers were more common after AMPT (five) than TVP (two) (*$\mathrm{P}=0{\cdot}29$*, n.s.). Dumping and diarrhoea were significantly commoner (*$\mathrm{P}<0{\cdot}001$*) after TVP, with 31 instances as opposed to eight with AMPT. The mean operating time was increased by 6 min when AMPT was performed rather than TVP. The results of this study have shown that AMPT is associated with a lower incidence of dumping and diarrhoea and achieves better overall Visick grading. However, continued monitoring is required to assess the long-term incidence of recurrent ulceration after this procedure.*

Keywords: Anterior lesser curve seromyotomy with posterior truncal vagotomy, truncal vagotomy and pyloroplasty, acid output, dumping, diarrhoea, recurrent ulceration

Although the number of elective operations performed for duodenal ulcer has declined in recent years, there has been no reduction in the number of major ulcer haemorrhages or perforations; indeed, the mortality rate from duodenal ulcer is increasing, particularly in the elderly[1]. Elective peptic ulcer surgery has been affected not only by the availability of the H_2-receptor antagonists but also by concern relating to the side-effects of truncal vagotomy[2] and the high rates of recurrence after highly selective vagotomy[3]. In 1979, anterior lesser curve seromyotomy and posterior truncal vagotomy (AMPT) was introduced as an alternative form of pylorus-preserving vagotomy[4]. We have now undertaken a randomized controlled comparison of the results of this operation and those of truncal vagotomy and pyloroplasty (TVP) over a 7-year period.

Patients and methods

One-hundred and forty-six patients with endoscopically proven chronic duodenal ulcer were selected for elective surgical treatment on the grounds of repeated severe symptoms during, or following, courses of H_2-receptors antagonists. Patients were randomized to undergo either TVP or AMPT. All operations were performed by one of the authors or a senior registrar. Once the surgeon judged the case to be suitable, an envelope was opened to ascribe randomization by a system of random numbers. Significant pyloric stenosis, as judged by symptoms of gastric stasis and/or the presence of a tight pylorus at operation, was regarded as an exclusion factor. The trial took place in three centres: the Manchester Royal Informary (75 cases), the Royal Preston Hospital (50 cases) and the Royal Liverpool Hospital (21 cases). Ethical committee approval for the study and informed consent were obtained. Patients were prospectively assessed concerning the duration and clinical features of their chronic ulcer disease and any history of bleeding or perforation. The duration of H_2-receptor antagonist therapy was noted, as were smoking and drinking habits.

Routinely, in two centres, gastric acid secretory function tests were performed both before and 2–3 months after surgery (90 patients). Such assessments were performed in response to both 0·2 units/kg intravenous insulin and 6 μg/kg subcutaneous pentagastrin stimulation. In Liverpool, a standardized test meal containing ^{99m}Tc-labelled bran in 100 g ReadyBrek® was utilized. Two egg sandwiches and a cup of tea brought the volume of the test meal up to 400 ml and calorific content to 475 calories. Emptying was assessed postprandially with the patient seated in front of a γ-camera computer system[5]. The duration of the operation and hospital stay, together with operative complications, were recorded on a proforma used by all centres and patients were assessed by participating consultants at 6 months, 1 year, and thereafter annually, according to a modified Visick system of grading[6]. Endoscopy was not routinely performed at follow-up but was undertaken in any patient in whom symptoms were suggestive of recurrent peptic ulceration.

Seventy-seven patients were allocated to AMPT and 69 patients to TVP. There were 115 men and 31 women in the study, with no significant difference in their distribution between the two operations. Of the women, 14 underwent AMPT and 17 underwent TVP. For the whole group, the mean(s.d.) ages were 45(13) years in the AMPT group and 45(15) years in the TVP group. The median duration of symptoms was 8·0 years in patients undergoing AMPT and 6·0 years in those undergoing TVP ($P=0{\cdot}05$). There was a previous history of bleeding in 13 patients in the AMPT group and seven in the TVP group. Perforation had occurred previously in four and eight patients in the two groups respectively. At the time of performing AMPT four patients underwent cholecystectomy, three had antireflux procedures and one had a splenectomy. One patient underwent both cholecystectomy and an antireflux procedure at the same time as TVP.

The median duration of H_2-receptor antagonist therapy was 2·8 years and 2·5 years in the AMPT and TVP groups respectively ($P>0{\cdot}05$). The mean(s.d.) duration of follow-up was 4·5(1·4) years after AMPT and 4·3(1·5) years after TVP (n.s.); the range of follow-up was 2–7 years. Non-parametric analysis was carried out using the Mann–Whitney *U* test, clinical grades were compared using the χ^2 test.

Table 1 *Comparison of acid secretory data after AMPT and TVP*

	Median acid output (mmol/h)		
	AMPT	TVP	P*
Before operation			
Basal acid output	2·3	2·3	>0·05
Insulin (0·2 units/kg i.v.) induced peak acid output	18·0	16·8	>0·05
Pentagastrin (6 μg/kg s.c.) induced peak acid output	30·4	22·4	>0·05
After operation			
Basal acid output	1·4	1·6	>0·05
Insulin (0·2 units/kg i.v.) induced peak acid output	2·5	2·08	>0·05
Pentagastrin (6 μg/kg s.c.) induced peak acid output	11·5	9·78	>0·05

AMPT, anterior lesser curve seromyotomy with posterior truncal vagotomy; TVP, truncal vagotomy and pyloroplasty; i.v., intravenous, s.c., subcutaneous; * Mann–Whitney *U* test

Results

There was one postoperative death which followed TVP in a 69-year-old man who developed congestive cardiac failure and pneumonia. Preoperative results of acid secretion and stimulated acid output in response to intravenous insulin (0·2 units/kg) and subcutaneous pentagastrin (0·6 μg/kg) between the two operative groups are shown in *Table 1*. Both procedures resulted in a similar percentage reduction in acid output in response to insulin administration, namely 87 per cent after AMPT and 89 per cent after TVP. The mean(s.d.) durations of operation were 53(10) min for AMPT and 47(10) min for TVP ($P=0{\cdot}2$, Mann–Whitney *U* test). The mean(s.d.) lengths of postoperative stay were also similar, namely 7·1(1·7) days after AMPT and 7·8(2·3) days after TVP.

Distension, a sensation of abdominal swelling or bloating, diarrhoea and dumping were all more common after TVP, with at least one of these problems affecting 31 patients after TVP as opposed to eight patients with AMPT ($\chi^2=21{\cdot}3$, $P<0{\cdot}001$). None of the patients described dumping after AMPT. One patient developed carcinoma of the stomach 2 years after TVP. Two antireflux procedures were performed after AMPT and two after TVP; one patient required reconstruction of the pylorus for severe dumping and diarrhoea after TVP; and three underwent cholecystectomy after TVP, although no patient required this procedure after AMPT where innervation of the gallbladder remained intact.

Gastric emptying studies were performed in 16 of the 21 Liverpool patients before and after the operation. After AMPT ($n=8$) emptying was essentially unchanged, with the exception of one patient who showed an initial delay ($t_{1/2}=72$ min) but when the study was repeated at 1 year emptying was normal. Following TVP, four patients showed more rapid emptying after operation ($t_{1/2}=5$, 23, 24 and 25 min) and one patient showed delay ($t_{1/2}=68$ min). The normal mean(s.d.) rate of emptying for this method is $t_{1/2}=55(10)$ min. One patient underwent endoscopically controlled balloon dilatation of the pylorus.

Endoscopically proven recurrent peptic ulceration occurred in five patients (6 per cent) after AMPT and in two patients (3 per cent) after TVP ($P=0{\cdot}29$, n.s.). All of these recurrences occurred within 2 years of the operation, four occurred in Preston and three in Manchester. Three of the five patients with recurrence after AMPT underwent antrectomy and two were treated medically; in the TVP group one patient was treated by antrectomy and one was treated medically. One patient in the AMPT group and one in the TVP group developed diarrhoea (defined as the passage of three or more loose stools daily or severe urgency of defaecation) following the second operation. Unsatisfactory results (i.e. Visick grades III and IV), occurred in 13 per cent of patients after AMPT and in 32 per cent after TVP (*Table 2*) ($\chi^2=6{\cdot}58$, $P=0{\cdot}01$).

Discussion

Over the past century numerous operations have been devised for the treatment of chronic duodenal ulcer[7]. Those that represent an aggressive attack on acid–pepsin secretion such as Pólya's gastrectomy have been associated with a high incidence of side-effects and an increased mortality rate, whereas the more conservative procedures have carried a high risk of recurrence[3,8–10]. Pylorus-preserving vagotomy has beyond doubt reduced the incidence of the incurable complications of dumping and diarrhoea and thus strengthened the case for more conservative surgery[11].

An attempt has been made to produce an operation which provides the greatest guarantee of gastric vagal denervation, while permitting preservation of the pylorus to minimize dumping and diarrhoea[4]. In AMPT the whole of the posterior gastric wall is denervated by the division of the posterior vagus trunk, while along the anterior wall the innervation of the antrum is preserved. Normal antral motility is thought to be preserved by transmission of impulses along the anterior nerve of Latarjet which, having reached the anterior antral musculature, are conducted to the posterior antral wall by intramural vagovagal arcs[12]. In conventional highly selective vagotomy it is the posterior parietal cell mass which is the most difficult area of the stomach to denervate, particularly because of fibres at the oesophagogastric junction and at the antral–corpus junction[13]. AMPT represents a smaller technical departure from TVP than does conventional highly selective vagotomy, and truncal vagotomy remains the most popular operation for chronic duodenal ulcer in the UK, possibly because it is simple, safe and speedily performed. It is for these reasons that AMPT was compared with TVP in this study.

Comparisons between AMPT and highly selective vagotomy have been made in a recent study of 91 patients from the Netherlands[14]. At periods of follow-up varying from 2 to 5 years the recurrent ulcer rates were 9·3 per cent after highly selective vagotomy and 8·7 per cent after AMPT. The degree of acid secretory inhibition was identical in both groups and diarrhoea and dumping were equally uncommon. The major difference was in operating time, which was halved by AMPT. The acid secretory inhibition achieved by AMPT is also maintained in the long term[4].

AMPT might, on theoretical grounds, be expected to have a higher incidence of diarrhoea and dumping than highly selective vagotomy because of denervation of the pancreas and small intestine[14,15]. In practice, this has not proven to be the case, either in our own or in the Dutch study[14]. Three factors potentially contribute towards dumping and diarrhoea: creation of the pyloroplasty, division of the hepatic branches of the anterior vagus nerve, and division of the coeliac branches of the posterior vagus nerve. Division of the posterior vagal trunk alone does not appear to play a major role in the development of so-called postvagotomy diarrhoea. Any diarrhoea that does occur after AMPT may be related to the effect of bacterial overgrowth due to a delay in gastric emptying,

Table 2 *Visick grading for AMPT and TVP*

	Visick grade*			
	I	II	III	IV
AMPT ($n=76$)	52	14	5	5
TVP ($n=68$)	25	21	19	3

AMPT, anterior lesser curve seromyotomy with posterior truncal vagotomy, TVP, truncal vagotomy and pyloroplasty, * when I+II are compared with III+IV, $\chi^2=6{\cdot}58$, $P=0{\cdot}01$

rather than to the direct effect of denervation of the pancreas and small bowel[16,17].

AMPT is an extremely safe operation. There has been no recorded incidence of ischaemic necrosis of the lesser curvature in over 700 operations[15]. Because the stomach is not opened, the procedure is associated with a low incidence of infection, lower than that which follows vagotomy and pyloroplasty The duration of the operative procedure is not significantly greater than that for TVP and is about one-half that for conventional highly selective vagotomy[14]. There were no deaths following AMPT in the present study, and after 700 operations we are aware of only one patient who has died in the postoperative period, the cause of death being myocardial infarction.

An occasional problem which has been associated with AMPT is delay in gastric emptying[17,18] Isotope tests of gastric emptying performed before and 3 months after surgery in eight of our Liverpool patients showed no significant delay and we have previously reported that gastric emptying after AMPT is essentially normal[16]. It is thought that the division of circular muscle along the myotomized segment of the stomach may compensate, to some extent, for the loss of adaptive relaxation[15,16] In our wider experience of the operation we have encountered symptomatic delayed gastric emptying which responded to a drainage procedure in 1 5 per cent of patients[15].

It has been largely as a result of ulcer recurrence rates that operations for duodenal ulcer either stand or fall Some recurrences are inevitable and are treatable by drugs or further surgical procedures, whereas the sequelae of dumping and diarrhoea are incurable. Gastrojejunostomy was safe, simple and had few postoperative sequelae, but floundered, almost half a century ago, on the grounds of high recurrence rates. Rates of recurrence exceeding 25 per cent, which have been reported in the long term after highly selective vagotomy, have aroused particular concern[3,8,9]. These rates are higher in the hands of the inexperienced surgeon[10] In the present study five recurrences occurred after AMPT compared with two after TVP and, although this was not significantly different, long-term monitoring is needed. However, one of the authors (T.V.T.), has been using AMPT for 10 years and only three late recurrences have occurred.

It is beyond dispute that a major decline has occurred in the number of patients undergoing elective duodenal ulcer surgery. On stopping treatment with H_2-receptor antagonists, the recurrence rate approaches 90 per cent at 1 year. Despite these drugs having been available now for 10 years, there has been no decline, indeed there has been a recent rise, in the mortality rate from ulceration, particularly in the elderly. There remains a limited role for elective peptic ulcer surgery and further research is required to iron out the remaining problems[19]. Perhaps, for example, division of the gastroepiploic vessels at the antral–corpus junction should be performed with AMPT (L. M Nyhus and E. Donohue, personal communication) and this has recently become our practice In addition, consideration should also be given to mucosal antrectomy, which would further reduce acid secretion[20] Several problems still remain to be solved in elective ulcer surgery but this study has shown that AMPT compares favourably with TVP.

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CA72-4: a new tumour marker for gastric cancer

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To date, tumour markers for gastric cancer have proved unreliable. In this study the value of a new serum marker, CA72-4, was compared with the serum activities of carcinoembryonic antigen (CEA) and CA19-9 in a consecutive series of patients with gastric cancer. The results show that the CA72-4 assay is significantly better at separating stage I and II disease from normal controls ($P<0\cdot01$) *than CEA (n.s.) or CA19-9 (n.s.). CA72-4 also gave better differentiation between patients with positive and negative nodes* ($P<0\cdot01$) *and between those who were serosa positive and negative* ($P<0\cdot01$)*. CEA differentiated between patients with positive and negative nodes* ($P<0\cdot05$) *but CA19-9 could not. CA19-9 and CEA could not discriminate between patients who were serosa positive and negative. In this study, at a specificity of 95 per cent, the sensitivities of CEA, CA19-9 and CA72-4 were 0·25, 0·41 and 0·94 respectively. These preliminary findings indicate that CA72-4 is a reliable tumour marker of disease stage and activity in gastric cancer. Further longitudinal studies are required for full evaluation of its clinical utility.*

Keywords: Stomach neoplasms, tumour markers, biological

Serum tumour marker concentrations have, in the past, proved unhelpful in the management of patients with gastric cancer Carcinoembryonic antigen (CEA) has been found to be elevated in 21–61 per cent of patients with gastric carcinoma[1–5] and CA19-9 is raised in 15–72 per cent of such patients[4,6–8]. The combination of these two tests does not significantly increase sensitivity[5]. The CA72-4 assay measures a high molecular weight, human tumour-associated glycoprotein, TAG-72, by a twin-site immunoradiometric assay using two different monoclonal antibodies: B72-3, raised against human breast carcinoma, and CC49, raised against purified TAG-72. B72-3 has a limited reactivity to normal tissue and fails to react to non-epithelial malignancies[9,10]. Recent reports examining serum CA72-4 and patients with gastric cancer have shown that TAG-72 is raised in between 33 per cent[11] and 59 per cent[12] of patients. The combination of CA72-4 and CA19-9 is reported to detect up to 70 per cent of patients with gastric cancer[12]. In this preliminary study serum CEA, CA19-9 and TAG-72 were measured in normal controls and in a consecutive series of patients with gastric cancer. The relationship between these tumour markers and the presence or absence of gastric cancer and its stage was examined.

Patients and methods

Thirty-nine control patients (with no history of malignant disease) and 33 patients with gastric cancer were studied (*Table 1*). Each patient had preoperative venous blood samples drawn Serum was separated within 1 h of collection and stored at −70°C until analysed. CEA was measured in a one-stage radioimmunometric assay using two specific monoclonal antibodies prepared against sterically remote antigenic sites (ELSA–CEA, CIS (UK), High Wycombe, UK). CA19-9, a recurring carbohydrate epitope which is a sialylated pentasaccharide of the Lewis A blood group, was measured by a two-stage radioimmunometric assay using solid phased and radiolabelled anti-CA19-9 (ELSA–CA19-9) TAG-72 was estimated by a solid phase, two-site, two-stage radioimmunometric assay using the two monoclonal antibodies CC49 and B72-3 (Centocor Incorporated, Malvern, Pennsylvania, USA). In the first stage the TAG-72 binds to CC49 and during the second stage ^{125}I-labelled B72-3 reacts with the already bound TAG-72 All specimen handling was carried out using a Tecan-903 (Tecan, Reading, UK) automated pipetting station; ^{125}I was counted using the Pharmacia Gamma Master (Pharmacia Ltd, Milton Keynes, UK); and data reduction was performed using RIAcalc (Pharmacia Ltd.). Each patient was staged according to the new tumour node metastasis (TNM) classification[13] (*Table 2*)

Statistical analysis was performed using the Mann–Whitney *U* test for group comparison.

Results

The results for tumour marker *versus* tumour stage are shown in *Figure 1*. In calculating an upper limit cut-off value for each of these markers, a value which included 95 per cent of the values of the normal population was used. Using this criterion, 91 per cent of the CEA readings (cut-off value <12·8 µg/l) for stage I and II gastric cancer fell below this cut-off value; for stage III and IV tumours the equivalent figure was 67 per cent. The cut-off value for CA19-9 was <32·4 kilounits/l, and 63 per cent of stage I and II gastric tumours and 57 per cent of stage III and IV tumours fell below this value. For CA72-4 (cut-off value <4·4 kilounits/l) the equivalent percentages were 5 per cent and zero. Using the Mann–Whitney *U* test, CEA and CA19-9 results for stage I and II disease were not significantly different from control values, while for CA72-4 there was a significant difference ($P<0\cdot01$) between the normal

Table 1 *Patient characteristics*

	Controls	Patients with gastric cancer
Number	39	33
Median age in years	66·7 (36–86)	65·5 (44–83)
Men·women	27:12	22·11

Values in parentheses show the range

Table 2 *Tumour node metastasis (TNM) classification*[13] *of patients with gastric cancer*

Stage	Ia	Ib	II	IIIa	IIIb	IV
No of patients	2	4	6	1	6	14
Groupings for analysis		12			21	

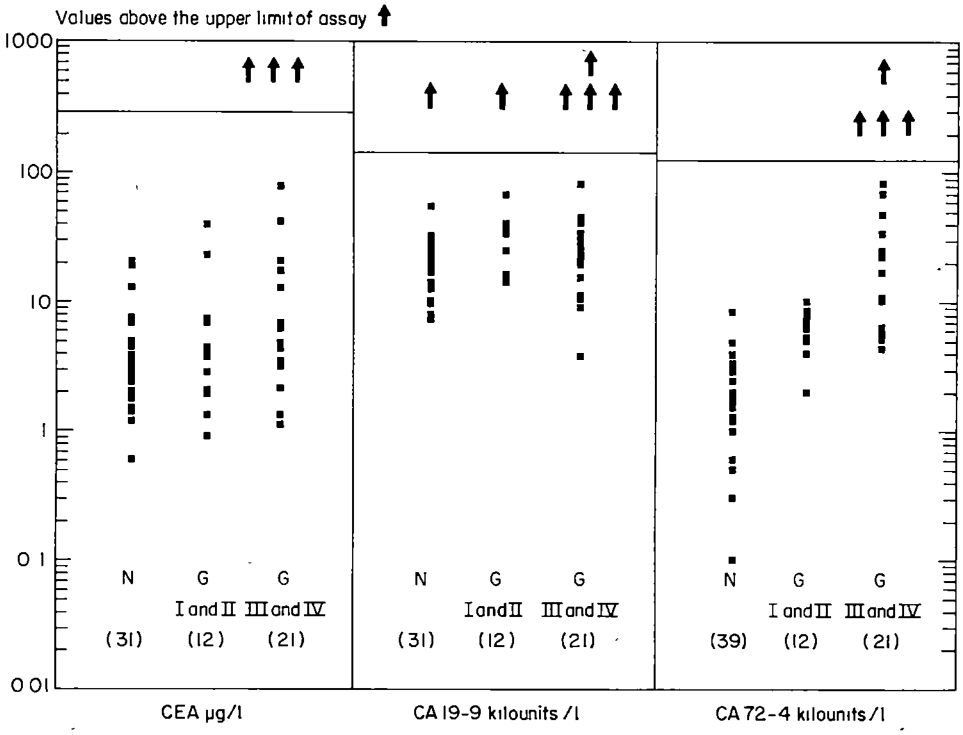

Figure 1 *Relationship between serum level of tumour markers and stage of gastric cancer. N, normal controls; G, patients with gastric cancer; CEA, carcinoembryonic antigen*

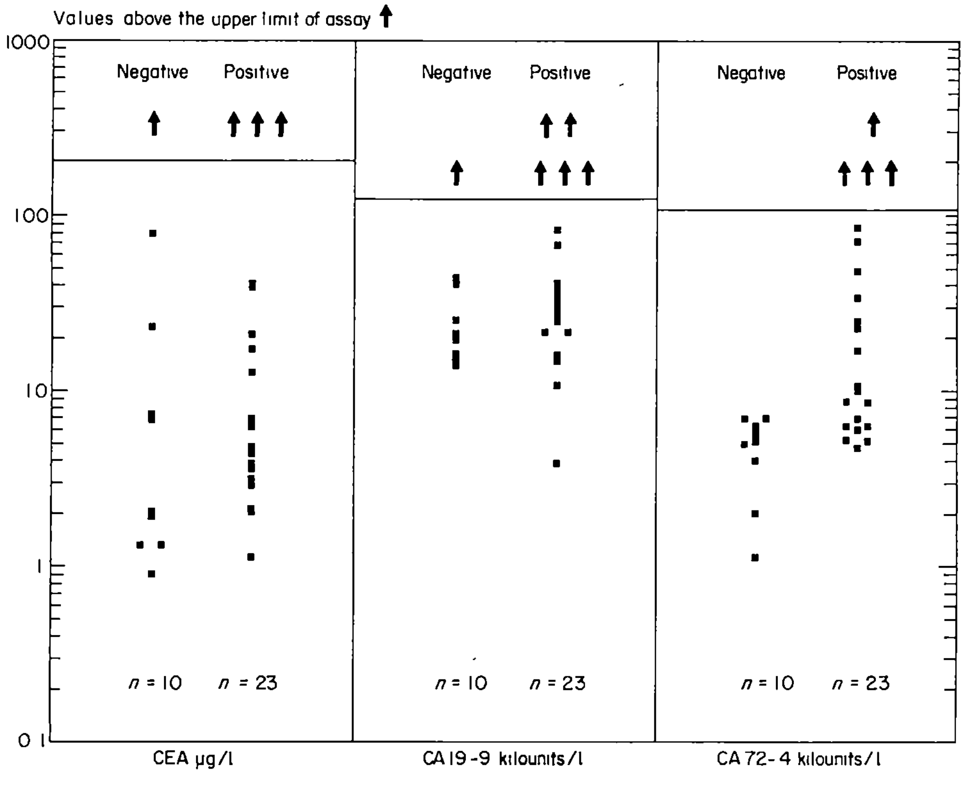

Figure 2 *Relationship between serum level of tumour markers and serosal involvement by gastric cancer. CEA, carcinoembryonic antigen*

controls and the stage I and II cancer patients. There was a significant difference between stage III and IV cancer patients and normal controls for CA19-9 ($P<0.05$), CEA ($P<0.01$) and CA72-4 ($P<0.01$).

At a specificity of 95 per cent, the sensitivities for identification of disease of CEA, CA19-9 and CA72-4 were 0·25, 0·41 and 0·94 respectively. When the results of these assays were analysed in relation to serosal involvement by tumour and histological lymph node deposits (*Figures 2* and *3*), the CEA values showed no significant difference between cases which were serosa positive or negative. A significant difference in the CEA levels ($P<0.05$) between those with negative or positive lymph nodes was seen. No significant difference was found between the CA19-9 results and serosal involvement or nodal status. Significant differences ($P<0.01$) were observed between those with serosal involvement and nodal status with

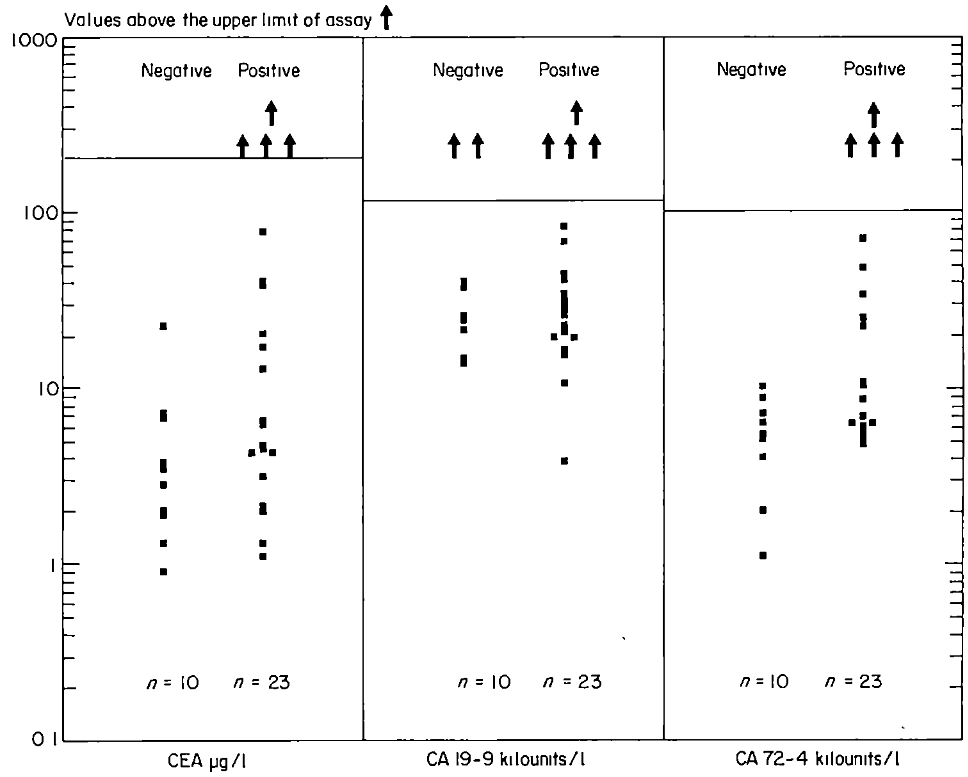

Figure 3 *Relationship between serum level of tumour markers and lymph node involvement by gastric cancer. CEA, carcinoembryonic antigen*

the CA72-4 assay. This tumour marker provided the best separation of the stage groups; its value in assessing disease progression was not enhanced by incorporation of the CEA and CA19-9 data.

Discussion

The various tumour markers which have been extensively investigated in patients with gastric cancer include CEA, CA19-9, CA50 and CA12-5[14]. None of these has been found to be useful when used singly either to detect tumour or to monitor disease activity. The combined use of some of these markers with other indices such as erythrocyte sedimentation rate, serum immunoglobulin G, C4 complement fraction and C1-esterase inhibitor has been reported to be more useful in predicting the presence of metastases and survival when assayed before operation[15]. The overlap between the stage groups limits the usefulness of these multifactorial assessments in monitoring disease activity and recurrence. It is the change in sequential results, however, which is of most importance when assessing recurrence, and a single sensitive tumour marker is preferable because it is easier to interpret and is more likely to be adopted in routine practice.

The data in this study suggest that the CA72-4 assay is significantly better than either CEA and CA19-9 in that it provides separation between stages of disease and correlates with the degree of mural invasion by tumour and histological lymph node involvement These results are in agreement with the findings of Heptner *et al.*[12] except that we did not demonstrate additional benefit by combining CA72-4 with CA19-9 or CEA.

Larger prospective longitudinal studies involving sequential assays of CA72-4 and adequate follow-up are necessary to establish the clinical utility of this tumour marker in terms of the clinical lead time of a rising CA72-4 level or its sustained elevation. Such a study involving three centres in the UK (Dundee, Birmingham and York) is in progress Early observations from this study are encouraging but require confirmation.

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Short note

Br. J. Surg. 1990, Vol. 77, September, 1013–1014

Primary gastric carcinoids: a view on management

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Primary carcinoid tumours of the stomach account for three out of every 1000 gastric neoplasms[1–4]. The tumours account for 2 per cent of all primary carcinoid tumours, are commonly multifocal, frequently metastatic (55 per cent of all the cases) and are associated with a high mortality rate (50 per cent at 5 years)[5] As a result many authors advocate a policy of aggressive surgical excision for all gastric carcinoids[1,6,7]. This paper reviews nine patients with primary gastric carcinoid.

Patients and methods

A survey of surgical and pathological records at St. James's Hospital, Dublin during the period 1979–88 revealed nine cases of primary gastric carcinoid From the charts and pathological records the sex, age at presentation, symptoms, investigations, pathological findings and treatment for each patient were recorded. The diagnosis of muscularis propria invasion was made on surgically resected specimens. Polypoid lesions that were completely excised histologically were considered not to have muscularis propria invasion. Follow-up and cause of death, where applicable, were ascertained

Results

Symptoms at presentation were all non-specific vague abdominal pain (four patients), anaemia (three patients), chest pain or heartburn (two patients), persistent nausea (one patient). The diagnosis was established by endoscopy and biopsy in all cases; only three out of eight barium studies demonstrated the lesion (*Table 1*).

Four patients presented with single, large (>4 cm), distal gastric tumours. None had associated gastric pathology. All four were treated by surgical excision. Three had muscle invasion and nodal involvement and died from tumour-related causes. The patient who underwent wedge excision had no evidence of muscle invasion or nodal involvement and is alive and well 15 months later.

Five patients had multiple (mean 9, range 4–12), small (mean 1·5 cm in diameter, range 0·5–3 0 cm) polyps. All were excised completely by endoscopic polypectomy. Two patients died from non-tumour-related causes and the other three are alive and well.

Discussion

The original description of carcinoid tumours was made by Langhans[8] in 1867. The first case of carcinoid tumours within the stomach was not reported until 1923[9]. Gastric carcinoid was first observed endoscopically in 1971[10] and was first confirmed histologically before operation by endoscopic biopsy in 1972[11].

Primary carcinoid tumours present as single or multiple polypoid lesions in the antrum of the stomach; they occur with equal frequency among men and women and are diagnosed most often during the sixth and seven decades of life. Clinical diagnosis is often difficult, the carcinoid syndrome is uncommon[12] and the gastric carcinoid syndrome resulting from histamine release occurs in very few cases[13]. Presenting symptoms are generally non-specific and preoperative diagnosis is usually established by endoscopic biopsy or polypectomy[14–16].

Table 1 *Patient details*

Patient no	Sex	Age (years)	Site of lesion	Average diameter (cm)	No	Muscle invasion	Treatment	Follow-up (months)	Outcome
1	F	36	Fundus	1	8	None	Polypectomy	72	Alive
2	F	66	Fundus	0 5	10	None	Polypectomy	48	Alive
3	M	57	Oesophagogastric junction	5	1	Yes	Total gastrectomy*	10	Dead†
4	M	62	Antrum	6	1	Yes	Total gastrectomy*	15	Dead†
5	F	60	Antrum	1	10	None	Polypectomy	72	Dead
6	M	79	Antrum	2	12	None	Polypectomy	48	Dead
7	F	67	Lesser curve	4	1	Yes	Partial gastrectomy*	5	Dead†
8	M	61	Lesser curve	6	1	None	Wedge excision	15	Alive
9	M	83	Antrum	3	4	None	Polypectomy	12	Alive

* Nodes positive; † dead from tumour

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The treatment of gastric carcinoid tumours has been shown to be dependent on many factors[16]. Most polypoid lesions up to 2 cm in diameter can be excised endoscopically using a snare. If the excision is complete and the histological findings show no malignant change, no further surgery is required and the patient may be followed up with regular endoscopic examinations. However, where lesions cannot be removed or where there is histological evidence of invasion, a total gastrectomy is recommended[6,7].

Although carcinoids are slow growing, they represent true malignancies with their rate of metastasis dependent on their site[5]. Sanders[17] reports the incidence of metastasis as 6 per cent for the appendix, 37 per cent for the small bowel, 36 per cent for the stomach and 63 per cent for the caecum and ascending colon. A recent report of ten cases of gastric carcinoids reported that 50 per cent had metastases[18]. In the absence of clinically obvious distant metastases, the preoperative diagnosis of malignancy may be based on histological evidence of muscle invasion Muscularis propria invasion was always associated with single large lesions. Multiple small lesions were easily excised and thus not associated with muscle involvement, and our experience suggests that they can be safely managed by endoscopic snare polypectomy. However, not all multifocal lesions are polypoid and consequently not all multifocal lesions can be treated endoscopically. In our study, muscularis propria invasion was always associated with a poor prognosis despite extensive surgical excision.

This study suggests that tumour size and the presence of muscle invasion are two important factors in the assessment and management of a patient with primary gastric carcinoid. The presence of muscle invasion has poor prognostic implications and the size of the lesion influences the surgical management. We suggest that small tumours (<2 cm in diameter) can be safely excised endoscopically. Larger lesions (>2 cm in diameter) without muscle involvement can be resected locally. Tumours with muscle invasion invariably have nodal involvement and have a poor prognosis despite aggressive surgery.

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Failure of nutritional recovery after total gastrectomy

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Malnutrition is reported to be an inevitable consequence of total gastrectomy, although there are few data to support this contention. Six patients of median age 63 years underwent total gastrectomy for malignancy. At follow-up (median 45 months, range 25–60 months) each patient was clinically tumour-free and underwent dietary assessment, faecal fat and nitrogen measurement and routine haematological testing. Protein and fat stores, measured by neutron activation analysis and the tritiated water dilution technique, were compared with the same measurements made before operation and with predicted values. Mean(s.d.) dietary intake (2224(381) kcal day^{-1} and 81(15)g protein day^{-1}) met the patients' estimated requirements. Mean(s.d.) serum albumin and faecal nitrogen values were normal but there was notable steatorrhoea (21(17) g day^{-1}). Body composition measurements revealed profound deficiencies of body-weight ($P<0{\cdot}02$), protein ($P<0{\cdot}01$) and fat ($P<0{\cdot}02$) before operation which were not corrected by an apparently curative total gastrectomy ($P<0{\cdot}05$), although further deterioration was prevented.

Keywords: Total gastrectomy, malnutrition, body composition

Despite the lack of recent supporting data, malnutrition is frequently reported to be an inevitable consequence of total gastrectomy. Suggested causes include inadequate calorie intake[1,2], malabsorption resulting from bacterial overgrowth[3,4] and pancreatic insufficiency[5]. It is also possible that malnourishment in these patients may be a result of the disease for which total gastrectomy was required (usually malignancy) rather than the surgery itself. We measured energy intake, faecal excretion of fat and nitrogen, body protein and fat stores, and performed routine haematological tests in six long-term survivors after total gastrectomy. Body composition results were compared with the same measurements made before operation and with predicted values.

Patients and methods

Four men and two women of median age 63 years (range 42–67 years) underwent total gastrectomy for adenocarcinoma (five patients) or lymphoma (one patient). A Roux-en-Y loop of jejunum was fashioned in five patients and a Hunt–Lawrence pouch was made in one patient. Body composition studies were performed on each patient before operation. Follow-up studies were performed a median of 45 months after surgery (range 25–60 months). Each patient was clinically tumour-free and had no dysphagia, reflux oesophagitis or other significant symptoms of disease.

Intake and excretion

A detailed dietary history based on 24-h recall and a 3 or 4-day food diary was taken by an experienced dietician. Faeces were collected over 3 days, fat was measured by solvent extraction and nitrogen by Kjeldahl analysis[6].

Haematology

Venous blood was taken for serum albumin, iron, iron binding capacity, vitamin B_{12}, folate, and 25-hydroxy calciferol measurement.

Body composition analysis

Prompt *in vivo* neutron activation analysis and the tritiated water dilution technique were used to measure total body protein and total body fat[7]. Predicted values were calculated from regression equations derived by direct measurement of total body protein and fat in 162 healthy volunteers from the local population, using age, height and sex for protein and age, height, sex and well weight for fat.

Analysis

Data were analysed using paired *t* tests.

Results

Dietary intake (Table 1)

The patients tended to take small frequent meals and achieved a mean(s.d.) daily energy intake of 2224(381) kcal, which was similar to their required intake of 2284(93) kcal, based on an estimated normal requirement of 40 kcal kg body-weight^{-1} day^{-1} (Reference 8). Carbohydrate intake was 301(75) g day^{-1} and fat intake was 90(37) g day^{-1}. Their protein intake of 81(15) g day^{-1} was not significantly different from the required 85·7(3·5) g day^{-1}, based on an estimated normal requirement of 1·5 g kg body-weight^{-1} day^{-1} (Reference 8). Fluid intake was 1500–2000 ml day^{-1}. Each patient received vitamin B_{12} supplements monthly.

Faecal excretion (Table 2)

Faecal fat excretion was raised in all patients (mean(s.d.) of 21(17) g day^{-1}; normal <5 g day^{-1}), representing 25(16) per cent of dietary intake. Levels in two patients were markedly raised (37 and 43 g day^{-1}). Faecal nitrogen was 6·4(2·9) per cent of dietary intake (normal 7·1(2·9) per cent[9]).

Haematology (Table 3)

Each patient had a normal serum albumin (mean(s.d.) of 43(1·7) g l^{-1}). Although serum iron was slightly low in two patients, neither was anaemic and serum iron binding capacity,

Table 1 *Daily dietary intake after gastrectomy*

	Mean	Range	Predicted value	*P*
Total energy (kcal)	2224(381)	1676–2710	2284(93	n.s.
Carbohydrate (g)	301(75)	190–380	–	
Fat (g)	90(37)	35–132	–	
Protein (g)	81(15)	61–98	85·7(3·5)	n.s.

Values in parentheses are s.d., n.s., not significant

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Table 2 *Daily faecal excretion after gastrectomy*

	Mean	Range	Normal value
Fat (g)	21(17)	7–43	<5
Nitrogen (percentage intake)	6·4(2·9)	2·4–10·0	7·1(2·9)

Values in parentheses are s.d.

Table 3 *Results of haematological tests after gastrectomy*

	Mean	Range	Normal
Serum albumin (g/l)	43(1·7)	41–45	35–47
Serum iron (µmol/l)	12(7)	6–24	10–30
Serum iron binding capacity (µmol/l)	66(7)	53–72	35–75
Serum B_{12} (pmol/l)	197(79)	113–287	135–700
Serum folate (nmol/l)	20(10)	10–39	5·4–18·3
Serum 25-hydroxy calciferol (µg/l)	30(9)	15–38	14–76

Values in parentheses are s.d.

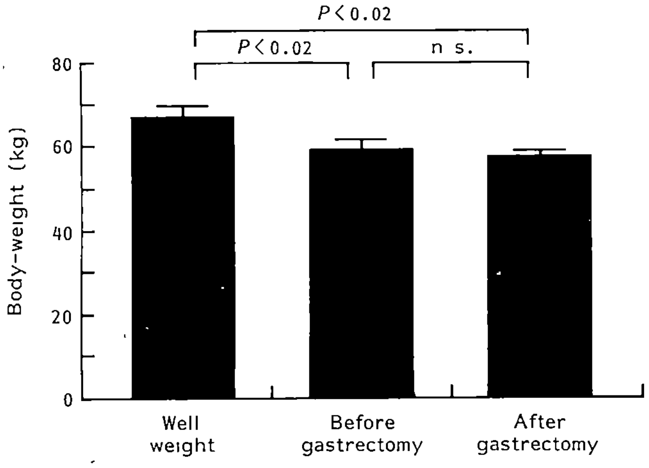

Figure 1 *Body-weight of six patients undergoing gastrectomy Values are mean(s.e.m.)*

vitamin B_{12} and folate were normal in all patients. 25-hydroxy calciferol levels were also normal (mean(s.d.) of 30(9) µg l^{-1}).

Weight (Figure 1)

Before total gastrectomy, mean(s.e.m.) body-weight was 59(3·7) kg, which was significantly lower than the recalled well weight of 66·5(3·3) kg ($P<0{\cdot}02$) Only one patient reported no weight loss before surgery. After an apparently curative total gastrectomy there was no significant weight change and mean(s.e.m.) body-weight (57·7(1·6) kg) remained significantly lower than the recalled well weight ($P<0{\cdot}02$).

Protein stores (Figure 2)

Before total gastrectomy, the mean(s.e.m.) total body protein value was 8·2(0·7) kg, which was significantly lower than the predicted value of 9·7(0·7) kg ($P<0{\cdot}01$). No significant change was demonstrated after operation and the mean(s.e.m.) value of 8·5(0·4) kg remained significantly lower than predicted values ($P<0{\cdot}05$).

Fat stores (Figure 3)

Before total gastrectomy, the mean(s.e.m.) total body fat value was 9·3(2·5) kg, which was considerably lower than the predicted value of 15·9(1·2) kg ($P<0{\cdot}02$). Two patients lost more than 75 per cent of predicted total body fat. Although the more severely depleted patients increased fat stores after total gastrectomy they did not approach their predicted levels. No significant change could be demonstrated in the group and the mean(s.e.m.) value of 10·1(1·3) kg remained significantly lower than predicted values ($P<0{\cdot}01$).

Discussion

These data show that before gastrectomy for malignant disease weight loss occurs as a result of loss of body protein and fat stores Although no improvement could be demonstrated years after an apparently curative total gastrectomy, surgery was able to prevent further deterioration in body-weight, protein and fat stores. Energy intake met the patients' requirements and protein intake and excretion were normal.

This failure to replenish body reserves may be related to the energy lost as steatorrhoea which was noted by us and others[3,10,11] A dietary solution to this problem would not be simple because malabsorption after gastrectomy is likely to be complex and multifactorial. The postgastrectomy reconstruction excludes food from the duodenum, which may result in inadequate mixing of food with bile and pancreatic enzymes[2,12]. The truncal vagotomy which accompanies total gastrectomy disrupts enteropancreatic reflexes and decreases mucosal release of cholecystokinin[5]. In addition, small intestinal transit time is shortened[13]. Bacterial overgrowth may result from the loss of gastric acidity or stasis in the afferent limb[13]. The resulting deconjugation of bile salts[14,15], together with rapid entry of food into the jejunum, may reduce the bile salt concentration below the critical level necessary for micelle formation and fat absorption.

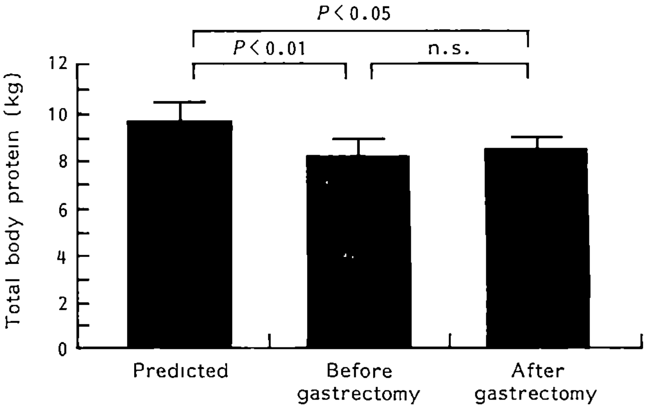

Figure 2 *Total body protein in six patients undergoing gastrectomy Values are mean(s.e.m.)*

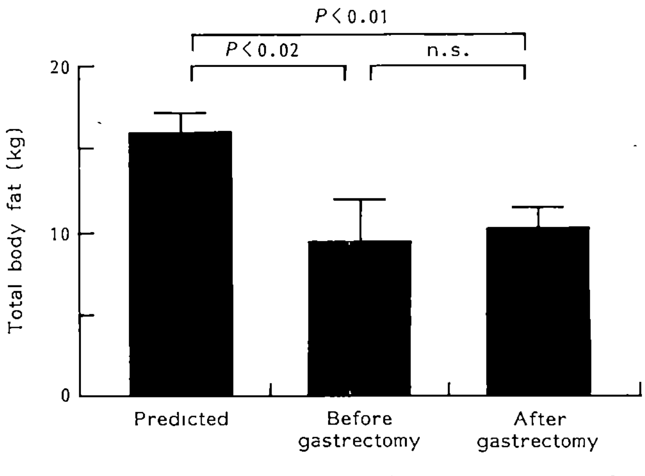

Figure 3 *Total body fat in six patients undergoing gastrectomy. Values are mean(s.e.m.)*

No patient studied had anaemia or hypoalbuminaemia. Osteomalacia can be a problem after gastrectomy but does not occur for several years. Serum 25-hydroxy calciferol levels in these patients were within the normal range.

We conclude that the malnutrition associated with total gastrectomy is a result of profound depletion of body reserves due not to the surgery but to the patient's disease (usually gastric malignancy). A curative total gastrectomy prevents further deterioration but recovery of protein and fat stores does not occur in spite of a normal energy intake. Steatorrhoea, the causes of which are multifactorial, may be a contributing factor.

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Feeding regimens after pyloromyotomy

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In a prospective randomized study three different feeding regimens after operation were compared in 74 babies with infantile hypertrophic pyloric stenosis: gradual regrading of feeds over 48 h (regimen 1), rapid regrading of feeds over 16 h (regimen 2), and initial starvation followed by full normal feeds at 24 h (regimen 3). No significant difference between the treatment groups was found either in episodes of vomiting after operation (regimen 1, 2·9 episodes in 21 patients; regimen 2, 3·6 episodes in 28 patients; regimen 3, 3·6 episodes in 25 patients) or in the mean duration of postoperative hospital stay (regimen 1, 59·3 h; regimen 2, 47·8 h; regimen 3, 56·7 h). We conclude that vomiting following pyloromyotomy is self-limiting and independent of the timetable or composition of the postoperative dietary regimen.

Keywords: Infantile hypertrophic pyloric stenosis, paediatric, feeding regimen, pyloromyotomy

Ramstedt's pyloromyotomy, preoperative resuscitation and modern paediatric anaesthetic techniques are the cornerstones of treatment for infantile hypertrophic pyloric stenosis[1]

A variety of different feeding regimens is used following pyloromyotomy[1]. Previous authors have considered the effect of these regimens in retrospective or uncontrolled studies, with varied conclusions[2,3,4].

Since normal gastric motility is not restored for 24 h following operation, the recommendation has been made that starvation for 24 h after operation is appropriate[5]

The optimum regimen for postoperative feeding remains unresolved. We report the first prospective, randomized, controlled trial comparing immediate, early and late feeding regimens after pyloromyotomy.

Patients and methods

All babies undergoing pyloromyotomy for infantile hypertrophic pyloric stenosis at the Wessex Regional Centre for Paediatric Surgery between March 1988 and August 1989 entered the study No patients with the condition were managed conservatively during this period.

During the phase of fluid and electrolyte resuscitation, all infants had a nasogastric tube passed for gastric lavage The tube was removed immediately after surgery.

No opiate premedications were used. All operations were performed under general anaesthesia using a transverse skin and muscle incision, followed by a standard Ramstedt pyloromyotomy. The infant was excluded from the trial if the mucosa was breached during operation. Premature infants were excluded.

No postoperative opiate analgesia was employed. A feeding regimen was selected at random from 60 shuffled, unmarked, folded sheets and the appropriate set of instructions was returned with the notes to the ward Feeding regimens are detailed in *Table 1*.

After operation the babies were kept in hospital until they tolerated their required fluids Intravenous fluid support was given until the first feed, then reduced to 5 ml per hour until oral feeding was established. They were all fed in a semierect position and nursed prone after winding The volume and frequency of feeds offered to the infants was not modified because of the pattern of vomiting. On the day after discharge, the infants' feeding notes were scrutinized and the number and timing of episodes of vomiting and the number of hours spent in hospital after operation were recorded

Results

Seventy-four patients entered the study, 64 males and ten females. Ten infants underwent pyloromyotomy during the study period and were excluded (eight were premature and two had the mucosa breached).

The mean admission weight was 3·89 kg (range 2·71–5·76 kg) and the mean age on admission was 40 days (range 14–112 days). Eighty-five per cent (63 out of 74 babies) were breastfed; there was no significant difference in breastfeeding between groups

Table 1 *Postoperative feeding regimens*

Hours after operation	Regimen 1	Regimen 2	Regimen 3
0–3	Nil by mouth	Nil by mouth	Baby is starved for 24 h after operation, then normal full-strength feeds are started
4–7	5 ml 5% dextrose hourly	40 ml 5% dextrose at 4 h	
8–10	10 ml 5% dextrose hourly	80 ml full-strength feed at 8 h	
11–13	10 ml half-strength feed/h	80 ml full-strength feed at 12 h	
14–18	15 ml half-strength feed/2 h	80 ml full-strength feed at 16 h	
20–22	30 ml half-strength feed/2 h	Normal feeding resumes	
24–26	30 ml three-quarters-strength feed 2 hourly		
28–30	30 ml full-strength feed 2 hourly		
32–34	45 ml full-strength feed 2 hourly		
36–42	60 ml full-strength feed 3 hourly		
45–48	75 ml full-strength feed 3 hourly		
	Normal feeding resumes		

Table 2 *Variation of postoperative vomiting according to feeding regimen*

	Feeding regimen		
	1	2	3
No of patients	21	28	25
No of breastfed patients	19	25	19
No of episodes of vomiting/ no of patients receiving regimen (vomiting episodes/child)			
No vomiting	– (5)	– (4)	– (5)
0–12 h	0·8 (11)	1·2 (19)	1·1 (9)
13–24 h	1·0 (13)	1·2 (13)	0·9 (13)
25–48 h	1·0 (11)	1·0 (16)	1·4 (10)
49–72 h	0·1 (3)	0·1 (3)	0·3 (4)
>72 h	– –	0·1 (1)	– –
Total vomiting episodes/ child	2·9 (16)	3·6 (24)	3·6 (20)

Values in parentheses denote number of children who did or did not vomit

Twelve patients underwent operation on the day of admission and the remaining 62 patients were operated on after a mean interval of 1·9 days. The classical findings of infantile hypertrophic pyloric stenosis were found in all the patients.

Table 2 shows the distribution of the episodes of vomiting within each group. There was no significant difference between the regimens either overall or in any particular time period. There was no significant difference between the regimens if the vomiting after 24 h was considered (χ^2). The hours between leaving the operating theatre and discharge from hospital were compared between the treatment groups using a Mann–Whitney U test. No significant differences were found (*Table 3*).

Discussion

This study shows that following pyloromyotomy vomiting is not influenced by the type of feeding regimen.

The cause of postoperative vomiting in infantile hypertrophic pyloric stenosis has been reviewed and diffuse gastritis has been implicated[3,6] although unsupported by histological evidence. An association between advanced oesophageal mucosal inflammation (secondary to gastro-oesophageal reflux) and postoperative vomiting is described[3]. Posture has also been cited as influencing postoperative vomiting[7].

Because postoperative starvation or conventional regrading produced no significant difference, the vomiting may be an extension of the natural history of postoperative infantile hypertrophic pyloric stenosis rather than a complication of pyloromyotomy or anaesthetic. This is supported by studies of gastric motility which show an increase in peristaltic activity and in the amplitude of pressure waves before operation which do not return to normal until 18–26 h after operation[5]. The time for the restoration of this normal gastric motility exceeds that for recovery from postoperative depression of peristalsis (motility studies[5] show a profound reduction in activity for 12–18 h). The resumption of normal feeding at 24 h is logical and earlier feeding has no benefit as demonstrated here and in previous reports[2,4].

Table 3 *Length of stay in hospital after operation*

	Feeding regimen		
	1	2	3
No. of patients	21	28	25
Mean(s.d.) hours per patient	59·3(11·7)	47·8(20·8)	56·7(23·8)

Standard deviation of difference of means: regimens 1+2=4·75, P=n.s.; regimens 1+3=5·78, P=n.s., regimens 2+3=6·38, P=n.s.; n.s., not significant

The rate of increase of feeding had caused controversy[2,8]. Our findings indicate no significant difference in vomiting whether a gradual regrading regimen or an immediate resumption of normal feeds is used. Discounting the first 24 h makes no difference to this conclusion. This study also demonstrates that the length of stay in hospital after operation is not influenced by the type of feeding regimen after pyloromyotomy.

Vomiting following Ramstedt's pyloromyotomy is independent of the timetable or composition of the postoperative feeding regimen.

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Treatment of adenocarcinoma of the cardia with synchronous chemotherapy and radiotherapy

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Twenty-nine evaluable patients with adenocarcinoma of the cardia were treated with synchronously administered chemotherapy (two cycles of 5-fluorouracil and cisplatin and 30–36 Gy of radiation to determine whether these tumours are responsive to such treatment. Complete regression of tumour was observed endoscopically in 19 patients, and partial regression in four. Fourteen patients had their tumours resected and in six no microscopic tumour was found in the specimen. Nine patients received additional radiotherapy to a total dose of 54–60 Gy instead of surgery. Tumour response was associated with rapid reversal of dysphagia. Only one patient required subsequent intervention for relief of dysphagia due to fibrous stricture. Enhanced survival was associated with a complete endoscopic response to initial chemotherapy and radiotherapy, and a tumour of <5 cm in length. The median survival of responding patients was 15 months. Synchronous chemotherapy and radiotherapy was of major palliative benefit in this series and merits further evaluation.

Keywords: Adenocarcinoma, cardia, synchronous chemotherapy and radiotherapy, surgery, palliation

The prognosis of patients with adenocarcinoma of the distal oesophagus and cardia continues to be poor, the 5-year survival rates ranging from 8 per cent[1] to 16·7 per cent[2] after resection. Surgery continues to be the traditional and only form of treatment to be offered to patients in an attempt to cure or achieve effective palliation. Radiotherapy and chemotherapy do not have an established role in the routine management of these patients. Indeed, there is a widely held view that radiation is not a worthwhile option for the treatment of these tumours in view of their assumed inherent radioresistance[3–5]

There are nevertheless reports that oesophageal adenocarcinoma can respond to irradiation[6,7] and that treated patients survive longer than those who are not treated[8] The addition of infusional chemotherapy with 5-fluorouracil to irradiation has been reported to provide effective palliation and control of disease in squamous cancer, and only recently a similar observation has been made on a group of 20 patients with adenocarcinoma using 5-fluorouracil and mitomycin C combined with irradiation[9].

Because of a favourable experience with a synchronous regimen of radiotherapy and chemotherapy in squamous cancer of the oesophagus[10], this approach was extended to adenocarcinoma of the cardia. The present paper describes our experience in 29 evaluable patients with adenocarcinoma who were treated with 5-fluorouracil infusion and cisplatin administered synchronously with irradiation, either before surgery or as the sole form of palliative treatment

Patients and methods

Patients

Thirty consecutive patients with biopsy-proven adenocarcinoma of the oesophagus or gastro-oesophageal junction were treated between October 1986 and December 1988 Tumours of the gastric fundus, even if in proximity to the cardia, were not included Mean(s d) tumour length was 5 7(3·4) cm (range 2–15 cm) Patients gave written informed consent and the protocol was approved by the Human Ethics Committee of the Royal Adelaide Hospital.

Initial evaluation

This included a barium swallow, chest radiography, flexible oesophagoscopy with biopsy and brushings for cytology, and computed tomography scanning of the thorax and upper abdomen Adequate hepatic, renal and bone marrow function was required and was demonstrated by biochemical and haematological screens and creatinine clearance Those who were considered medically unfit received further chemotherapy and radiotherapy to a total dose of 54–60 Gy according to the initial protocols Patients with metastatic disease received initial treatment to 36 Gy only

Radiation technique

Parallel opposing portals were used to deliver a total midplane dose of 36 Gy in 18 daily increments over 3 weeks. The portals incorporated known macroscopic tumour, 5 cm of normal oesophagus on either side of the visible tumour together with the relevant draining lymph nodes In the case of lower third tumours, they were the coeliac nodes, in upper third tumours, they were the supraclavicular and mediastinal nodes. Patients were reviewed weekly during treatment. If a severe reaction occurred therapy was interrupted until reactions subsided to a level where therapy could resume. One additional fractional dose was added for each treatment interruption amounting to 1 week

Follow-up evaluation

Patients were reviewed every 3 months. Endoscopy was performed at the first 3-monthly assessment and regularly thereafter when possible or if indicated by a recurrence of symptoms. Computed tomography scans were performed at 6-monthly intervals or when clinically indicated.

Response of the primary tumour to treatment was initially monitored by the clinical relief of symptoms and was regarded as a complete response if there was disappearance of tumour on endoscopy with mucosal healing and absence of tumour on biopsy Response of malignant disease to treatment was determined according to standard World Health Organization criteria[11].

Resection of tumour was undertaken in 15 patients. Seven patients were considered medically unfit for surgery and eight had extensive disease at presentation Nine patients received a full course of 54–60 Gy to the primary tumour, while in six cases with metastases no further treatment was given after the initial 36 Gy if symptoms had been relieved or the patient's general condition contraindicated it.

Statistical analyses

The association of different variables with treatment in patients without metastases was determined using the log rank test. These variables

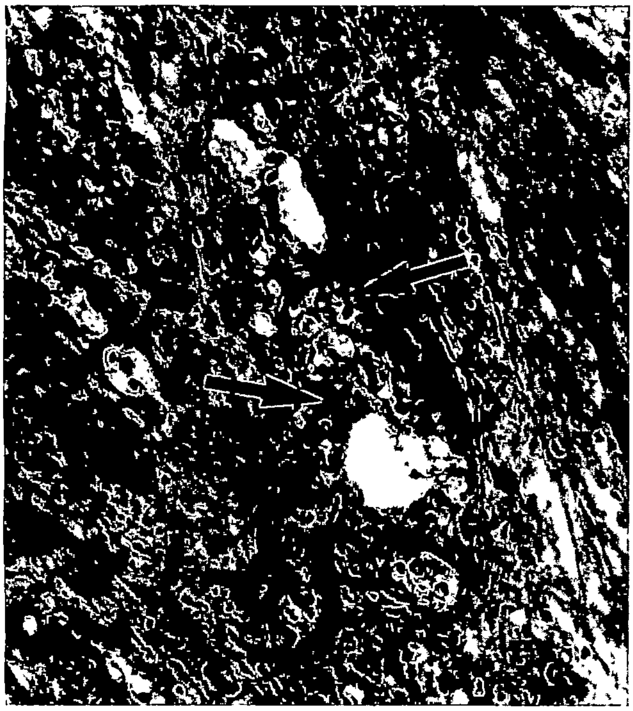

Figure 1 *Histological appearance of a resected primary tumour showing nests of necrotic tumour cells centrally (arrowed) with surrounding fibrosis and a scanty infiltration with chronic inflammatory cells*

included the patient's age and sex, the tumour length, response to chemotherapy and radiotherapy, nodal status, radiotherapy dose, and surgical *versus* non-operative treatment

Results

Response to initial treatment

Patients were reassessed endoscopically and radiologically 4 weeks after completion of an initial course of chemotherapy and 30 or 36 Gy of radiation. Nineteen of 29 evaluable patients (one patient died from an unrelated cause before treatment was complete) had complete tumour regression, four had partial regression (i.e more than a 50 per cent reduction in estimated tumour size) and in six there had been no change. Complete endoscopic responses were confirmed by oesophageal biopsy. Tumour regression was accompanied by relief of dysphagia and the ability to eat a normal diet

Of the 15 patients who had surgery, 14 underwent resection and one had a bypass procedure only due to the presence of liver metastases. Histological examination of the resected specimens confirmed the endoscopic finding of absence of tumour in six patients A further five patients were assigned a partial response following histological examination of the resected specimens in which microscopic tumour was found in the oesophageal muscle coat. In two of these patients the tumour cells were infrequent and appeared necrotic as a result of preoperative treatment (*Figure 1*).

Correlation between endoscopic and histological findings at operation

These findings are shown in *Table 1* which reveals an imperfect relationship between the two criteria of response The three patients who were assessed endoscopically as complete responders, but who were finally classified as partial responders, had no macroscopic evidence of tumour at operation. Foci of microscopic disease were found in the oesophageal wall on repeated microscopic examination of these specimens.

Outcome of therapy in surgical patients

Of the 15 surgical patients, ten had a complete endoscopic response after chemotherapy and radiotherapy immediately before surgery. All but one patient underwent oesophagectomy (the remaining patient had a substernal bypass with a cervical oesophagogastrostomy). Two patients died from cardiac causes in the early postoperative period and two patients developed anastomotic leaks, but both survived. Surgery and anaesthesia were not considered to have been compromised by the preoperative treatment, and in ten patients there was no macroscopic evidence of tumour at operation Six patients are alive, five free from disease and one with metastases at follow-up which ranges from 6 months to 21 months. In patients who achieved complete endoscopic regression of the macroscopic disease, the median survival was 14 8 months.

Outcome of therapy in patients treated with chemotherapy and radiotherapy alone

Fourteen patients who refused (two) or who were judged unfit for surgery (12) received treatment to 36 Gy (five patients) or 60 Gy (nine patients). One additional patient was not evaluable due to his death from a stroke which was thought to be due to an unrelated cause before completion of treatment.

Nine patients achieved a complete endoscopic response of the primary tumour to initial treatment and early relief of dysphagia. Partial regression was noted in two patients and no response in three. Five of these patients also had either liver (four) or lung (one) metastases at presentation and in two of these cases the metastases partially regressed during treatment.

Tumour recurrence

Of the 29 evaluable patients, ten are still alive at follow-up ranging from 3 to 21 months, three with liver metastases and seven free from disease.

Eight of the 14 patients who had their tumour resected died from metastatic disease which developed outside the radiotherapy field. Two of these patients, one of whom had known residual disease after operation, also had recurrence within the field and developed recurrent dysphagia. The remaining six had no local recurrence and retained normal swallowing until their deaths.

Fifteen patients were not resected (including the one patient who had bypass surgery) and eleven have died Three patients failed to respond to initial treatment and died within 1–3 months, and one died from unrelated disease before treatment was completed Ten patients achieved a complete response, of whom four are alive at 7, 11, 13 and 20 months respectively, while six have died from distant metastases without evidence of recurrence at the primary site. One patient also died from uncontrolled primary and metastatic disease after attaining a partial response. Of the total of eleven patients in this group who achieved a partial or complete response, none has required palliative intubation or dilatation to maintain swallowing after completion of treatment.

Morbidity of treatment

Treatment was well tolerated. Mild oesophagitis was experienced by all patients towards the end of treatment, and this was easily controlled by sucralfate. In two patients oesophagitis was severe and treatment was interrupted, but resumed in both cases. Nausea was mild in seven patients, moderate in seven others, but severe in none. No significant

Table 1 *Relationship between endoscopic response of primary tumours and histological response in resected specimens of 14 patients*

	Endoscopic response		
Histological response	Complete	Partial	No change
Complete	6	–	–
Partial	3	2	–
No change	–	–	3

bone marrow suppression occurred warranting modification of treatment during therapy.

Factors significantly affecting the outcome of treatment

The only two variables which were significantly associated with survival of more than 12 months after treatment were the endoscopic response to initial therapy (complete response *versus* partial response, $P=0{\cdot}032$) and tumour length (<5 cm *versus* >5 cm, $P=0{\cdot}018$).

The median survival of those attaining a complete response to initial chemotherapy and radiotherapy was 15 months compared with 6 months for those who did not achieve a complete response The survival of patients who were treated surgically after chemotherapy and radiotherapy did not appear to be different from those treated with further chemotherapy and radiotherapy, although the two groups were not comparable.

Both of these two groups of patients fared better than those patients who received the initial 36 Gy only and no other treatment, but again the groups are not strictly comparable and the numbers are too small to permit comparison

Discussion

Most patients with oesophageal adenocarcinoma have advanced disease at presentation and the main aim of treatment is relief of dysphagia with minimal treatment morbidity. This paper describes a method of treatment which has been used with good effect in squamous cell cancers[10] but appears to be equally effective in adenocarcinoma.

The results described in the present series confirm the finding by Coia *et al* [9] that adenocarcinomas of the cardia are markedly sensitive to synchronously administered chemotherapy and radiotherapy. They observed a high complete endoscopic regression rate in 20 patients with adenocarcinoma and a median survival time of 15 months in a group of patients who were not suitable for surgery and who were treated with 5-fluorouracil and mitomycin and radiotherapy. Our findings are almost identical but also allow an opportunity to observe the effects of treatment in surgical specimens, which revealed small persistent foci of tumour in patients who were judged to be free of tumour by all other criteria including oesophageal biopsy. The regression of tumour in our patients was accompanied by relief of dysphagia, and permitted normal swallowing for the duration of the patient's life in most instances. No patient in this series required intubation, although one required dilatation of a benign stricture.

These results have been achieved with acceptable morbidity and support the conclusion that synchronous chemotherapy and radiotherapy have a definite role in the palliative treatment of patients who are not suitable for, or who refuse, surgery. In view of the complete histological eradication of tumour in some cases, it may also offer some patients the prospect of long-term survival, comparable with that achieved by surgery alone in the short term, although this preliminary series does not specifically address this question. The persistence of tumour cells, however, in patients with complete endoscopic regression emphasizes the current place of surgery in curative treatment. The assessment of any impact of synchronous chemotherapy and radiotherapy on survival will require large-scale clinical trials comparing it with radiotherapy or surgery alone.

The potentially important place of synchronous chemotherapy and radiotherapy in the palliation of adenocarcinoma of the cardia and distal oesophagus is apparent when it is compared with the literature results of other treatments currently available. The importance of the capacity to swallow is repeatedly emphasized in the literature as the goal of palliative therapy and the main determinant of the patient's quality of life A recent paper by Desa *et al.*[12] emphasized this and reported a very high rate of complications in patients following oesophageal intubation. Other authors have confirmed the high incidence of problems with intubation. Such problems include a high mortality rate from the procedure, frequent food obstruction, recurrent dysphagia and the necessity for tube replacement[13,14] and have resulted in the conclusion that intubation is neither a safe nor a satisfactory method for palliation[14] This bears out the view that tumours of the oesophagogastric junction are anatomically unsuitable and difficult to intubate[15].

Surgical bypass has also been advocated and was used in one patient in the present series; however, it suffers the disadvantages of significant mortality and morbidity risk while swallowing frequently does not improve as well as expected[16,17] Furthermore in one report, a large number of patients (11 of 24) required repeated dilatation of the anastomoses after operation[17].

Radiotherapy given alone has not been effective in producing marked and durable regression of tumours. Eeftinck *et al.*[18] described their results in a large series from Rotterdam. All their patients with adenocarcinoma received 40 Gy before operation and they observed no effect on the histological staging and tumour morphology in the surgical specimens, nor any apparent effect on patient outcome. In the series of Desa *et al.*[12] there was a high rate of subsequent readmission for intubation and other procedures among the patients treated with radiation alone Gignoux *et al.*[19], reviewing the results of trials of preoperative radiotherapy administered alone in oesophageal cancer, commented upon the very low rate of complete responses obtained in these studies Thus the addition of synchronous infusional chemotherapy in our series and in that of Coia *et al* [9] appears to have had a marked radiosensitizing effect and to have contributed to tumour regression. We recognize, however, that the exact contribution of chemotherapy can be defined only in prospective randomized studies.

Endoscopic treatment using the NdYAG laser is being introduced in many centres to relieve dysphagia but the reported outcome is still imperfect as patients often require multiple treatment sessions, the duration of good palliation varies widely, and intubation is still required for a significant proportion of patients[20] We have found, like Coia *et al.*[9], that synchronous chemotherapy and radiotherapy produced regression of primary tumours and relief of dysphagia in the majority of patients and that further intervention for recurrent dysphagaia was rarely required. Cytotoxic drugs can often be given on an out-patient basis and hospitalization thus kept to a minimum.

As a result of using this treatment the number of palliative intubations overall in our institution has declined from 41 in the period 1982–85 to 12 between 1986 and 1989, emphasizing its value and its acceptance by the local medical community as a worthwhile treatment in this disease.

The role and impact of the chemotherapy on tumour regression remains uncertain, although comparison with the literature reports on the effect of radiotherapy alone (discussed above) suggests a significant enhancement of the effect of radiation In the longer term chemotherapy had no obvious effect on the development of the systemic metastases that were responsible for the majority of deaths. Continued administration of chemotherapy following completion of regional treatment may assist in controlling systemic micrometastases. Despite these limitations, currently available regimens of chemotherapy and radiotherapy, such as that reported in this paper, may have substantial benefit in the palliative treatment of oesophageal adenocarcinoma, and our results indicate that continued evaluation of combined modality treatment of this condition is justified.

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Short note

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Gastric outlet obstruction now predicts malignancy

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Pyloric stenosis used to be a frequent presentation of duodenal ulcer. Conversely, duodenal ulcer was the commonest cause of gastric outlet obstruction, accounting for 60 per cent of cases[1,2]. However, in the last 10 years the incidence of gastric outlet obstruction secondary to duodenal ulceration has declined, a change which has coincided with the widespread use of H_2-receptor antagonists There has also been a reduction in the incidence of gastric cancer and a changing location of gastric adenocarcinoma away from the antrum towards the cardia[3,4].

This study reports the changes in incidence of benign and malignant gastric outlet obstruction in a unit with a special interest in pyloric stenosis secondary to duodenal ulceration. We also record a prospective study of patients with gastric outlet obstruction in a district general hospital to determine the current relationship between these two causes of the condition.

Patients and methods

All patients who presented with symptoms or signs of gastric outlet obstruction to the Professorial Surgical Unit at Westminster Hospital from 1962 to 1985 were recorded prospectively. These records were reviewed and the final diagnosis in each case was classified as duodenal ulcer, other benign condition, gastric adenocarcinoma or other malignancy The figures up to 1975 have already been published[2] These figures cannot be related to population incidence, as many patients were referred from elsewhere

All patients presenting to the Department of Surgery at Kingston Hospital with symptoms and signs of gastric outlet obstruction from 1st October 1987 to 30th September 1988 were also analysed prospectively. Demographic, clinical, radiological and endoscopic details were recorded and compared with operative and pathological findings. The hospital serves a population of 179 400

Results

In the review series there were 252 patients. Up to 1975 there were 204 patients, of whom 123 had duodenal ulceration and 12 had another benign condition. There were 65 cases of gastric cancer and four other malignant conditions From 1976 to 1985 there were 22 cases of gastric outlet obstruction secondary to duodenal ulceration and two due to other benign causes There were 24 cases of gastric cancer.

The results of the prospective study are shown in *Table 1*. There were two cases of benign duodenal ulceration and seven in which gastric outlet obstruction was secondary to adenocarcinoma of the stomach (five patients), duodenum (one patient) or pancreas (one patient).

Discussion

Since the introduction of H_2-receptor antagonists to the UK market in 1977, there has been a dramatic reduction in the incidence of operation for duodenal ulceration, but the incidence of perforation and bleeding appears to be unaffected[5,6] Changes in the incidence of gastric outlet obstruction secondary to duodenal ulceration have not been reported previously.

Even though it is now recognized that the incidence of gastric cancer is declining, our observed fall in the number of patients with benign stenosis was much greater than the change in gastric cancer This has resulted in a reversal of the ratio between benign and malignant causes of gastric outlet obstruction, so

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Table 1 *Clinical features and diagnosis at different stages in the management of nine patients with gastric outlet obstruction*

Patient no	Sex	Age (years)	Symptoms	Duration (months)	Signs	Clinical	Radiological	Endoscopy	Operative
1	F	72	Vomiting, epigastric pain, weight loss >5 kg	2	Mass	Duodenal ulcer	—	Duodenal ulcer	Duodenal ulcer
2	F	78	Vomiting, bleeding, weight loss >5 kg	2	—	Recurrent duodenal ulcer	Duodenal ulcer	Pyloric canal ulcer	Duodenal ulcer
3	M	57	Epigastric pain, back pain, weight loss >5 kg	6	Succussion splash, palpable stomach	?Duodenal ulcer, ?carcinoma of stomach, ?nodal metastases	Intrinsic or extrinsic carcinoma of second part of duodenum	—	—
4	M	76	Vomiting, weight loss >5 kg	5	Succussion splash, palpable stomach, mass	Carcinoma of stomach	—	Carcinoma of stomach	Inoperable carcinoma of stomach
5	M	81	Vomiting, epigastric pain, weight loss >5 kg	2	Mass	Carcinoma of stomach	Gastric outlet obstruction, ?cause	Carcinoma of stomach. Histology positive	Carcinoma of stomach
6	M	64	Nausea, epigastric pain	6	Succussion splash	Gastritis, ?benign stenosis	Pyloric obstruction, ?metabolic	Carcinoma of stomach. Histology positive	Carcinoma of stomach
7	F	76	Vomiting, epigastric pain, weight loss >5 kg, reflux oesophagitis, constipation	6	Succussion splash	Benign stenosis	Pyloric obstruction, ?cause	Pyloric canal ulcer, histology = carcinoma of stomach	Carcinoma of stomach
8	F	34	Epigastric pain, bleeding	14	Succussion splash	Pyloric canal ulcer	—	Pyloric canal ulcer	Inflammatory mass Histology = carcinoma of stomach
9	F	57	Epigastric pain, back pain, constipation, fullness	1·5	Succussion splash	Benign stenosis	Benign stenosis	Duodenal stricture	Carcinoma of duodenum

that we found an excess of malignant causes of 3·5 1. The current predominance of malignancy as a cause of gastric outlet obstruction has not, to our knowledge, been recognized before now.

The findings in the prospective study bear out the changes in incidence and demonstrate the frequency of incorrect diagnosis. Of the seven cases of malignancy, the correct clinical diagnosis was achieved in only two patients. Radiology was incorrect in four of the five cases of malignancy in which barium studies were performed. Endoscopy achieved a correct diagnosis on macroscopic appearance in only three patients. In one further patient the endoscopic biopsy showed the presence of carcinoma Two further patients wrongly diagnosed endoscopically as having a pyloric canal ulcer and duodenal stenosis were not biopsied

There were three patients in whom the clinical picture suggested carcinoma. In four patients with malignancy, in whom there was no clinical suggestion of carcinoma, radiology was unhelpful. Endoscopy made the correct diagnosis in two of these cases. It seems likely that if biopsy had been performed in all cases of gastric outlet obstruction, then the rate of correct preoperative diagnosis could have been improved.

We have demonstrated a falling incidence of benign gastric outlet obstruction. Malignancy is the predominant cause of this presentation. All patients with gastric outlet obstruction should now be considered to have malignancy until proved otherwise. Endoscopic biopsy is indispensable in the management of this condition.

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Manometric evaluation of jejunal limb after total gastrectomy and Roux–Orr anastomosis for gastric cancer

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Total gastrectomy with Roux–Orr anastomosis is frequently performed for gastric cancer. Since intestinal motility of the Roux limb has never been evaluated after this operation, pressure activity was investigated in the Roux limb of ten patients (aged 51–77 years) who had undergone total gastrectomy and Roux–Orr reconstruction. Investigations were carried out during a 6-h fast and 3 h after a 605 kcal mixed meal. During fasting only two patients had activity fronts and these were abnormal. All ten patients displayed non-propagating bursts of contractions and three had discrete clustered contractions and high amplitude jejunal contractions. The fed state was characterized by a severely reduced motor activity pattern and other abnormalities. Total gastrectomy with Roux–Orr anastomoses provokes a relatively severe disturbance in intestinal activity.

Keywords: Gastrectomy, intestinal, manometry, motility

The surgical approach to gastric cancer frequently involves total gastric excision followed by anastomosis of the oesophagus to the small bowel[1,2]. The most widely used surgical procedure is that reported by Goldschwend[3] in 1908, using the technique proposed by César Roux and modified by Orr[4].

There is evidence that most gastric operations provoke motor disturbances and that symptoms such as abdominal pain, nausea, vomiting and diarrhoea occur in up to 30 per cent of patients[5,6]. Motor function has been evaluated in various subsets of gastrectomized patients[7–11] but manometric studies after total gastrectomy are rare and of short duration[12]. There are no studies on the effects of total gastric resection on small bowel motility[13]. A scintigraphic study in patients who had undergone total gastrectomy and Roux-en-Y reconstruction demonstrated that solid food passed rapidly from the gullet to the Roux limb and then became uniformly distributed throughout the long portion of the small bowel; transit time was prolonged[14]. In Italy, gastric cancer is often treated by total gastrectomy with Roux–Orr anastomosis[2,15]. However, this may result in troublesome abdominal symptoms[9,16].

Manometric studies have been performed to evaluate motor behaviour of the reconstructed limb in both fasting and fed conditions after total gastrectomy.

Patients and methods

Ten consecutive patients (six men and four women of mean(s.d.) age 63(7) years, range 51–77 years) who had undergone total gastrectomy for gastric cancer with end-to-side Roux-en-Y anastomosis were studied. The length of the Roux limb was about 50 cm. Manometric evaluation was carried out at least 1 year (mean(s.d.) 25·4(2·8) months) after surgery. All operations had been done by the same surgeon. No patient had detectable signs of cancer recurrence at the time of manometry, as judged by physical examination, blood chemistry, abdominal ultrasound scan, total body computed tomography scan, barium meal (to exclude obstruction at the level of the anastomosis) and endoscopy (to document no or only minimal inflammation of the distal oesophagus). Clinical characteristics are given in *Table 1*. Each patient gave informed consent to the investigation.

A 7-lumen manometric probe (Arndorfer Medical Specialties, Gleendale, Wisconsin, USA) with a tungsten-weighted tip and recording points at 7, 27, 37, 47, 48, 49 and 50 cm from the tip was used. Each lumen was connected to an external physiological pressure transducer (Bell and Howell Sensormedics Italia, Milan, Italy, type 4-327-1) and was constantly perfused with bubble-free distilled water at a rate of 0·5 ml/min by a low compliance system[17]. At this perfusion rate, the system yields a pressure rise to distal occlusion of more than 200 mmHg/s. Intraluminal pressures were recorded on a multichannel Beckman R-611 Dynograph recorder (Sensormedics Italia), with a paper speed of 0·25 mm/s.

After an overnight fast the manometric probe was inserted through the nose to within the Roux limb. It was positioned under fluoroscopic control such that the four proximal, closely spaced recording points straddled the oesophagojejunal anastomosis, while the distal three points lay in the jejunum (*Figure 1*).

Once the probe had been positioned, recording began immediately and lasted for 6 h during fasting and for 3 h after consuming a 605 kcal standard mixed meal composed of rice (60 g) with olive oil (20 g), roast veal (100 g), boiled green beans (100 g), and stewed apples (200 g), with 18·2 per cent protein, 36·2 per cent lipids and 45·6 per cent carbohydrates. Patients were encouraged to eat as much of the meal as possible, at least as much as they ate at home, so that intestinal motor activity could be recorded under near normal conditions.

Table 1 *Clinical features of manometrically evaluated patients with total gastrectomy and Roux–Orr anastomosis*

Patient no.	Age (years)	Sex	Bowel function	Upper gut symptoms
1	56	F	Diarrhoea, constipation	–
2	51	M	–	Dysphagia, food regurgitation, bile vomiting
3	68	F	–	Abdominal pain (rare)
4	59	M	Diarrhoea (rare)	Dyspepsia (rare)
5	57	F	Diarrhoea (rare)	Dysphagia, pyrosis (rare)
6	77	M	Diarrhoea	Dysphagia
7	61	M	Diarrhoea (rare)	Dysphagia, pyrosis (rare)
8	69	M	Diarrhoea	Pyrosis, dyspepsia
9	65	M	Diarrhoea (frequent)	Bile vomiting, pyrosis, bile regurgitation
10	66	F	Diarrhoea	Bile regurgitation, nausea, abdominal pain, abdominal distension

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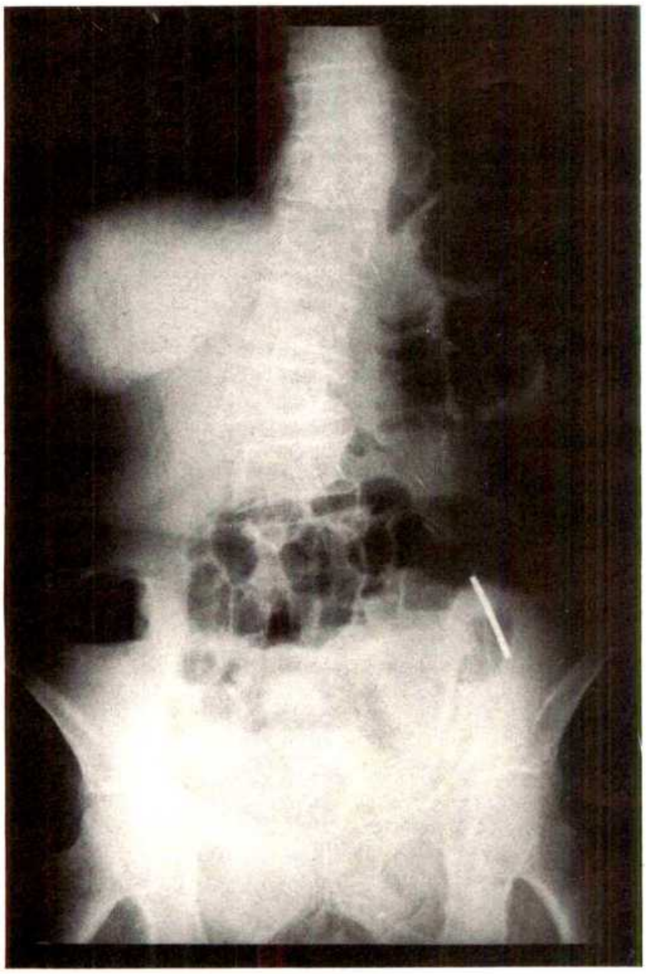

Figure 1 *Abdominal radiograph showing the manometric probe* in situ. *Side openings are located at the level of the metallic plugs*

Manometric analysis

Manometric tracings for fasted and fed periods were visually analysed by one of the authors. The fasting period results were similar to those previously described[18-22]. The cyclic variations of motor activity, i.e. the migrating motor complexes (MMCs), were identified. Briefly, phase I is characterized by motor quiescence, phase II by irregular but persistent contractions, and phase III (activity fronts) by bursts of rhythmic contractions, propagated in a oroaboral direction, which last at least 3 min and occur at a maximum frequency in the intestinal segment under observation (10–11 per min for the jejunum). The following specific motor abnormalities were looked for[23-26]: aberrant propagation and/or configuration of activity fronts; bursts of non-propagated phasic pressure activity (defined as phasic pressure activity lasting for at least 2 min with amplitude >20 mmHg and frequency of contraction of 10–12 per min); and discrete clustered contractions (defined as groups of phasic waves with amplitude >15 mmHg, occurring at a rate of 10–12 per min and duration of about 1 min, often with some tonic elevation, preceded and followed by at least 30 s of quiescence).

The fed period has been described previously[22,24,27]. The postcibal intestinal motor pattern was defined as short bursts of irregular, random contractions interspersed with transient, brief periods of quiescence. Previous studies from this laboratory have shown that the meal described above elicits a continuous fed motor pattern for the entire 3-h postprandial period in healthy subjects[22,28].

Results

Manometric features are summarized in *Table 2*. During the fasting period eight patients displayed no MMC activity. Abnormal (simultaneous onset, retropropagated or irregularly propagated) activity fronts occurred in the remaining two patients (*Figure 2*). Non-propagated bursts of contractions (*Figure 3*) were noted in all ten patients. Unusually prolonged (>1 min in one patient) high amplitude (>80 mmHg) contractions (*Figure 4*) and discrete clustered contractions (*Figure 5*) were recorded in three patients.

During the fed period overall intestinal motor activity was rare and was represented by low amplitude contractions (*Figure 6*). Non-propagated bursts of contractions were registered in four patients postprandially, and early (within 60–90 min of eating) activity fronts were seen in three. Two patients also displayed early postprandial high amplitude (>80 mmHg) contractions.

Discussion

There are few data on intestinal motility in patients subjected to gastric resection[12,13] and the effects of total gastric resection with Roux–Orr anastomosis have never before been investigated by manometric techniques. In the present study most patients complained of upper and/or lower bowel disturbances. Manometric investigation revealed major motor abnormalities in the Roux limb in all patients in both fasting and fed states.

Table 2 *Manometric features*

Patient no.	Fasting state	Fed state
1	No MMC activity; non-propagated bursts	Consistent motor response for only 42 min. In the late postprandial period, non-propagated bursts
2	Frequent (about every 15 min) irregularly propagated activity fronts; non-propagated bursts	No consistent motor response; early (within 30 min) postprandial vomiting
3	No MMC activity; non-propagated bursts	Nausea while eating; minimal postprandial activity; early (within 60 min) phase III activity front
4	No MMC activity; non-propagated bursts	Accentuated response; phase III-like non-propagated activity in the late postprandial period
5	No MMC activity; non-propagated bursts; sporadic high amplitude contractions; discrete clustered contractions	Early postprandial high amplitude contractions associated with abdominal pain; thereafter, low amplitude contractions with sporadic baseline elevation
6	No MMC activity; non-propagated bursts	Low amplitude postprandial activity; non-propagated bursts
7	No MMC activity; non-propagated bursts	Scarce response to food ingestion; three activity fronts (two with simultaneous onset) in the early (within 80 min) postprandial period
8	Non-propagated bursts; three abnormal (simultaneous onset) activity fronts	Very scarce response to food ingestion; non-propagated postprandial bursts
9	No MMC activity; non-propagated bursts; frequent high amplitude contractions; discrete clustered contractions	Early postprandial high amplitude contractions; thereafter, non-propagated postprandial bursts
10	No MMC activity; non-propagated bursts; frequent high amplitude prolonged contractions; discrete clustered contractions	Good response of the first few cm of the jejunal limb, whereas the distal portions showed very minimal activity

MMC, migrating motor complex

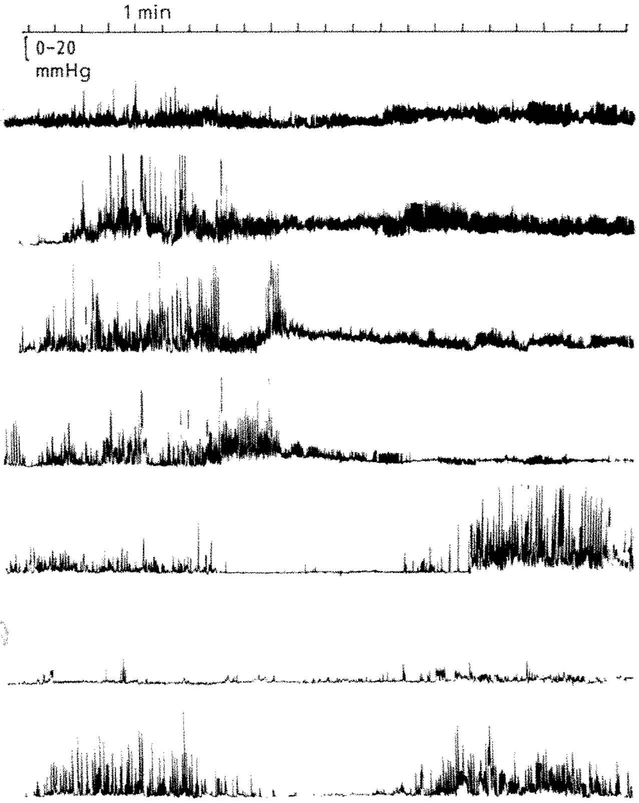

Figure 2 *Manometric tracing showing irregularly propagated phase III activity fronts during fasting. The first four recordings are from the oesophagojejunal anastomosis; the last three are from the Roux limb*

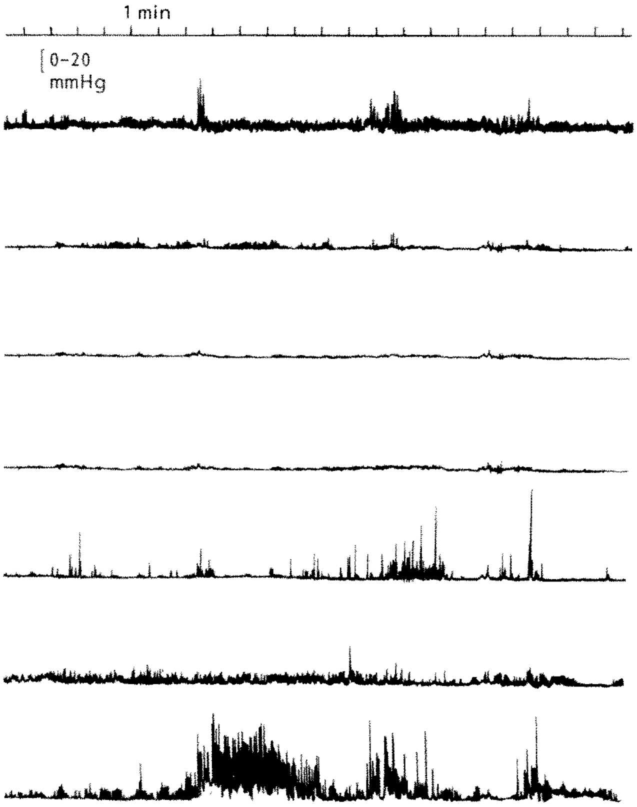

Figure 3 *Representative manometric tracing showing non-propagated bursts of contractions in the Roux limb. Recording points are as in* Figure 2

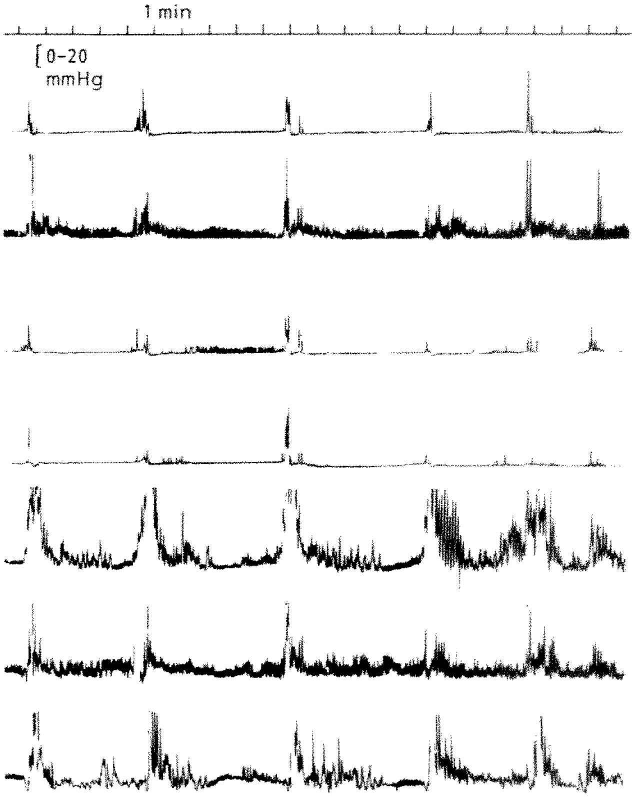

Figure 4 *High amplitude prolonged jejunal contractions recorded in the Roux limb in a subject. Note that some of the contractions last for more than 1 min. Recording points as in* Figure 2

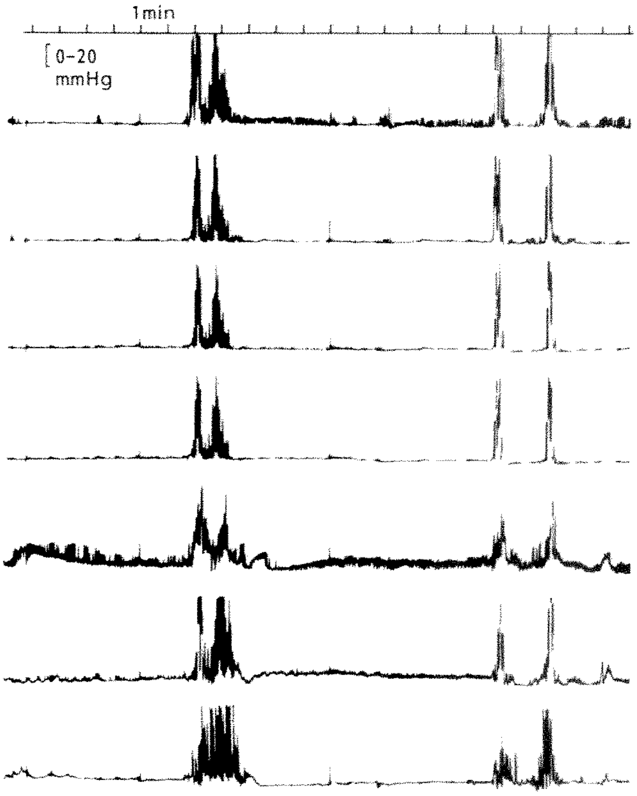

Figure 5 *Representative manometric tracing showing discrete clustered contractions. All recording points are in the Roux limb*

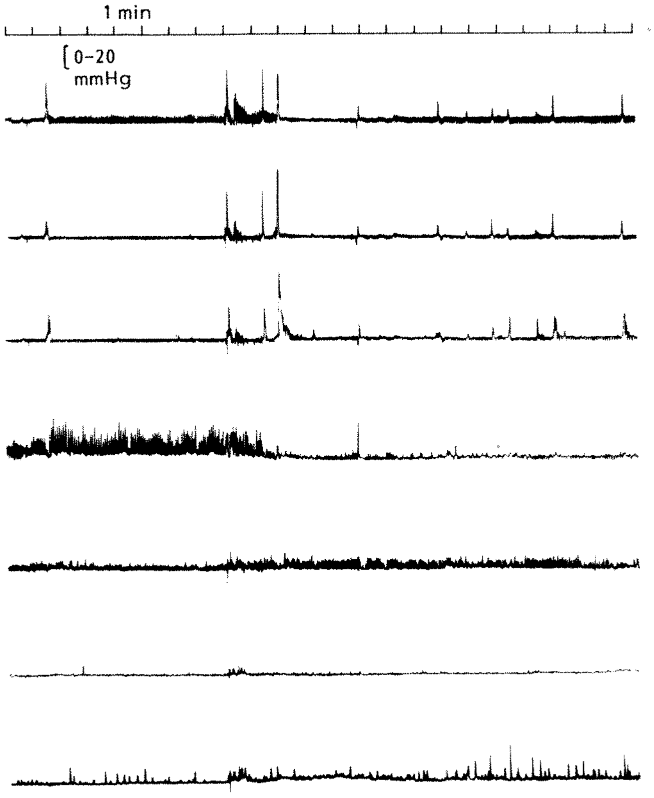

Figure 6 *Postprandial manometric tracing showing minimal contractile activity of the Roux limb after the standard meal had been consumed. Recording points are as in* Figure 2

Motility pattern alterations have been reported after Billroth II surgery[8,9]. However, whereas MMCs (albeit abnormal) were documented in all Billroth II patients, activity fronts were recorded in only two patients in the present study and both were abnormally propagated. Non-propagated bursts of contractions were observed in all ten patients during fasting, and in four postprandially. Three subjects also displayed prolonged and discrete clustered contractions, probably due to surgical intervention, which were believed to be responsible for symptoms.

The Roux limb is an isolated segment of jejunum that is not under appropriate electrical control[9]. Given that isolated intestinal segments may show pacemaker function[29–31] and that a limited portion of the small intestine has been demonstrated to be able to pace the remaining small bowel[32,33], it may be that the Roux limb for some reason behaves as a functionally obstructing intestinal segment.

Although vagotomy disrupts the fed pattern in humans and animals, studies in both have shown that vagotomy has little influence on the MMC[34,35]. Moreover, Thiry–Vella loops (intestinal segments without continuity with the remaining bowel) are still able to generate MMC activity[36]. Finally, experiments in dogs have shown that MMCs are preserved after total gastrectomy, but that the initiation of a fed pattern has a shorter latency after the operation[37]. Hence, the motor abnormalities observed in the Roux limb after total gastrectomy in humans probably have a complex pathophysiological basis that cannot be satisfactorily explained in our present state of knowledge.

In conclusion, this study shows for the first time that patients with total gastrectomy and Roux–Orr anastomosis have significant motor abnormalities in the reconstructed intestinal limb in both fasting and fed conditions. These abnormalities are probably responsible for the upper and lower gut symptoms reported by the patients and, especially in the early period after operation, could account for the various bowel disturbances of which virtually all patients complain.

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Case report

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Glyceryl trinitrate in the management of a biliary fistula

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Biliary leakage after cholecystectomy is not uncommon[1]. It is accepted teaching that in an adequately nourished patient with no active disease and no distal obstruction, fistulae will close spontaneously. We report a case of a postcholecystectomy fistula which resolved when distal obstruction due to presumed sphincter spasm was relieved by the use of glyceryl trinitrate.

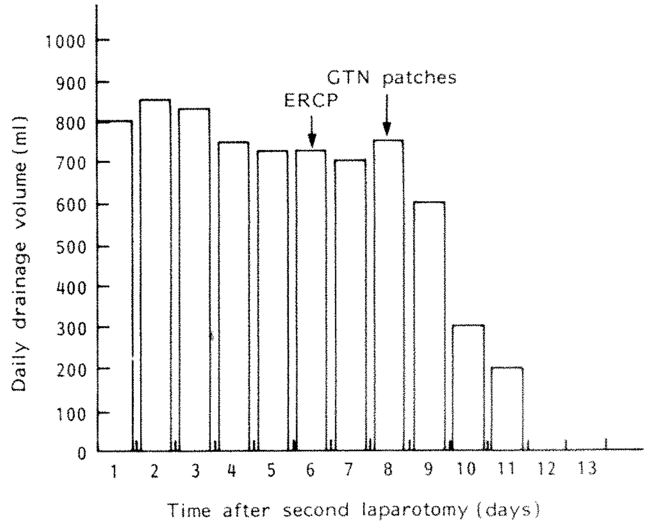

Figure 1 *Volume of bile-stained fluid recovered from an intra-abdominal drain after second laparotomy. ERCP, endoscopic retrograde cholangiopancreatography; GTN, glyceryl trinitrate*

Case report

An obese 46-year-old man gave a 12-year history of abdominal pain due to proven gallstones. Cholecystectomy proved difficult because the gallbladder was firmly adherent to surrounding structures. A fundus first dissection was performed and during dissection in Calot's triangle the cystic duct was avulsed from the common bile duct. This was repaired primarily without narrowing and a tube drain was placed in the hepatorenal pouch.

In the 2 days after operation there was no drainage and the patient was well. When the drain was removed on the second day 300 ml of bile-stained fluid escaped from the drain site. Two days later the patient complained of right hypochondrial pain and ultrasonography demonstrated a small intraperitoneal collection. This was treated conservatively and the patient appeared to settle. He was well enough to return home at 10 days but returned a week later complaining of abdominal pain and distension. Ultrasonography revealed an increased amount of intraperitoneal fluid and a ^{99}Tc-Sn-2,6-diethylacetanilido-iminodiacetate (HIDA) scan showed continued leakage of bile from the common bile duct. A second laparotomy was performed and 3 litres of bile-stained fluid was aspirated. Drainage was re-established but the common bile duct was not disturbed.

Over the next 6 days drainage was between 700 and 800 ml per day (*Figure 1*). Endoscopic retrograde cholangiopancreatography (ERCP) showed continuing leakage but no stricturing or retained stone. Contrast failed to drain from the bile duct during the examination and spasm of the sphincter of Oddi was diagnosed. Drainage from the intra-abdominal drain was unchanged by ERCP. Before offering endoscopic sphincterotomy, glyceryl trinitrate was administered in the form of a trinitrin patch in a dose of 5 mg per day (Transiderm-Nitro®, Ciba Laboratories, Horsham, UK). Following this the fistula output declined rapidly to zero (*Figure 1*).

Discussion

In the present case it is probable that spasm of the sphincter of Oddi prevented fistula closure. In such a situation endoscopic sphincterotomy may be used to good effect but in our patient this was not needed following the use of glyceryl trinitrate. The delay in response after ERCP suggests that the eventual fall in fistula output is a genuine result of pharmacological relaxation of the sphincter. This medication is eaily administered in a slow-release form and is known to induce sphincter relaxation[2]. It may prove to be a practical alternative to endoscopic sphincterotomy with its attendant morbidity and mortality rates.

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Single lumen ileum with myectomy: a possible alternative to the pelvic reservoir in restorative proctocolectomy

An alternative procedure to construction of a pelvic ileal reservoir was assessed which avoids the need for a pouch, while providing an adequate rectal substitute and good continence. Thirty-six female adult beagles were allotted randomly to undergo total colectomy with (a) ileo–anal anastomosis alone, (b) ileo–anal anastomosis with two 15 cm myectomies, (c) ileo–anal anastomosis and myectomy with an ileo–ileal valve, or (d) ileo–anal anastomosis with a duplicated J pouch. The animals were studied before operation and at 4-weekly intervals for 20 weeks after operation. Mortality rates were similar. Ileal compliance was increased significantly by myectomy from 0·64 ml/mmHg (median, interquartile range 0·49–0·78) after ileo–anal anastomosis alone to 1·65 mmHg (1·16–1·93), $P<0\cdot01$, *an increase which was maintained. Ileal capacity was also increased both by myectomy and by the J pouch: ileo–anal anastomosis = 85 ml (75–100 ml), ileo–anal anastomosis and myectomy = 139 ml (116–156 ml), ileo–anal anastomosis and myectomy and ileo–ileal valve = 125 ml (range 85–145 ml), ileo–anal anastomosis and J pouch = 130 ml (range 75–165 ml)* ($P<0\cdot01$). *Bowel function in the other three groups was markedly superior to ileo–anal anastomosis alone. Mean transit time was significantly less after ileo–anal anastomosis, 5·2 h (2·6–8·2 h) than after both ileo–anal anastomosis and myectomy, 10·5 h (9·6–13·9 h),* $P<0\cdot05$ *and ileo–anal anastomosis and J pouch, 11·0 h (8·4–13·0 h),* $P<0\cdot05$, *but addition of an ileo–ileal valve did not produce a further increase in transit time, 12·9 h (range 10·5–14·5 h),* P = *n.s.. Myectomy of single lumen ileum may be a useful alternative to a pelvic ileal reservoir in restorative proctocolectomy.*

Keywords: Ulcerative colitis, ileoanal anastomosis, myectomy, pelvic reservoir, anorectal manometry, intestinal transit

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Panproctocolectomy with a permanent ileostomy has remained the standard surgical treatment of ulcerative colitis for over 50 years. Though it cured the disease, the inevitable ileostomy frequently led to physical and psychological problems. To eliminate the ileostomy, Parks and Nicholls[1] combined the concept of an ileo–anal anastomosis[2–4] with that of an ileal reservoir[5,6], and the subsequent refinement of their procedure in the past decade has made it the operation of choice for young patients with ulcerative colitis[7]: anal continence is preserved, the ileostomy abolished and there is no perineal wound, while bladder and sexual problems are virtually eliminated[8].

Nevertheless, the results of restorative proctocolectomy still leave much room for improvement. The procedure fails in 5–10 per cent of patients who are left with a permanent ileostomy. In many of the others the functional result is marred by minor faecal leakage, difficulty in emptying the reservoir, or 'pouchitis', with frequency and urgency of bowel action. Moreover, the operation is still attended by much morbidity, in the form of pelvic sepsis[9], anastomotic dehiscence, stricture and small bowel obstruction.

The operation of straight ileo–anal anastomosis without a pelvic reservoir[3,4] has been abandoned by most surgeons because of the excessive bowel frequency that results from the low compliance and capacity of the ileum and its excessive peristaltic drive[10]. This procedure is less complicated and time consuming, however, than restorative proctocolectomy with a pelvic reservoir. Our hypothesis was that a capacious and compliant rectal substitute could be fashioned from single lumen ileum by weakening the muscular wall of the ileum by means of myectomy. The consequent increase in its compliance and capacity should improve the functional result of straight ileo–anal anastomosis. While this is not a new idea[11–14], it has been little explored. We wondered, too, whether placing a valve in the ileum proximal to this ileal 'neorectum' might slow intestinal transit, prevent bacterial contamination of the upper small bowel[15] and thus improve the clinical result. For comparison with these experimental procedures we chose the duplicated J pouch because it is simple to construct, widely used in man and has been shown in a prospective trial[16] to give clinical results as good as the quadruplicated W reservoir.

Materials and methods

The experimental studies were carried out in 36 fully grown female beagles. They were dewormed and observed for 1 month before operation to make sure that they had no concurrent illness. In each dog the following parameters were assessed: general health, weight, perianal cleanliness, stool consistency and frequency, haemoglobin concentration, haematocrit, platelet count and white blood cell concentration.

The operation was performed after the dogs had fasted overnight. No preoperative bowel preparation was used. Medazalam (1 mg/kg

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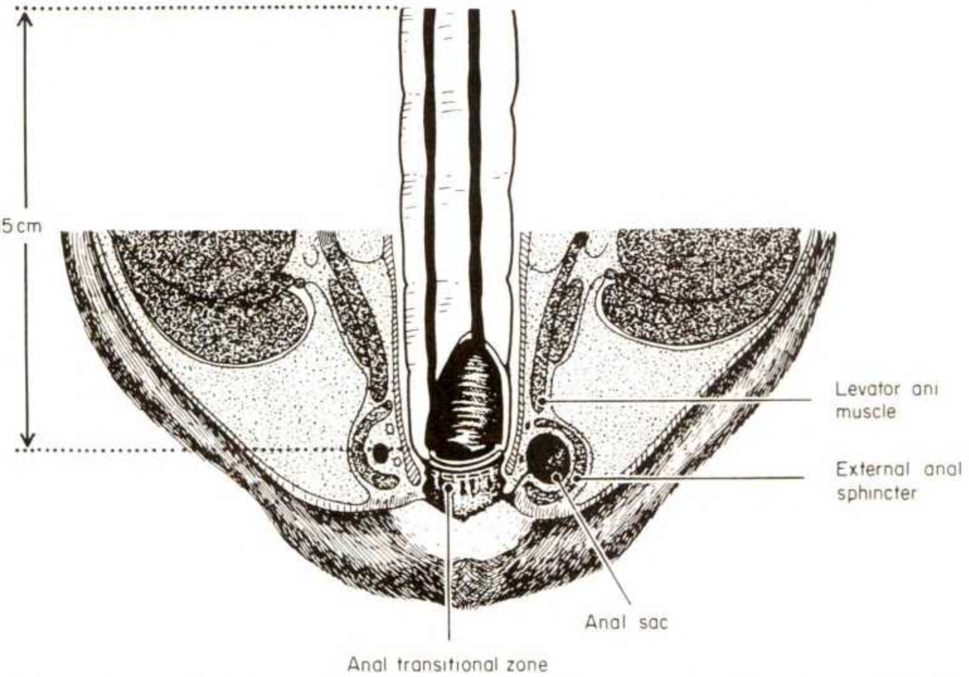

Figure 1 *A coronal section of the pelvis of the dog with double myectomy of single lumen ileum. The ileum is anastomosed to the top of the anal canal*

intramuscularly) and atropine sulphate (25 µg/kg subcutaneously) were administered 1 h before operation. Anaesthesia was induced with an intravenous infusion of methohexitone sodium (10 mg/kg) and maintained with a mixture of halothane, nitrous oxide and oxygen. Dextrose saline was infused intravenously during the operation and bolus doses of ampicillin (500 mg), gentamicin (80 mg) and metronidazole (500 mg) were given at the start of the laparotomy. No further antibiotics or crystalloid infusions were given after operation unless the clinical condition of the animal dictated otherwise.

Operative procedures

The animals were allotted in random fashion to one of four operative procedures:

1. Straight ileo–anal anastomosis (n = 9). Proctocolectomy was performed through a midline incision. The ileum was transected just proximal to the ileocolic valve and the rectum transected at the anorectal line. Continuity was restored by an end-to-end anastomosis between the terminal ileum and the upper anal canal. A purse-string suture was inserted into the divided anal stump and an Ethicon 21 mm stapling instrument (Ethicon Ltd., Edinburgh, UK) used to construct the anastomosis.

2. Ileo–anal anastomosis with myectomy (n = 9). Proctocolectomy with ileo–anal anastomosis was performed as described above. Before the anastomosis was constructed, however, two 15 cm strips of smooth muscle and serosa were removed from the ileum. The myectomies commenced 2 cm proximal to the divided end of the bowel. The strips were about 0·75 cm in width and were situated on either side of the bowel, each being at 120° from the mesenteric border (*Figure 1*). This left an intact strip of ileal wall along the antimesenteric border.

3. Myectomy and ileal valve (n = 9). After proctocolectomy, two myectomies were constructed as in group 2. In addition, an ileo–ileal valve as described by Grosfeld *et al.*[17] was fashioned just proximal to the myectomies. The plane between the inner circular and outer longitudinal muscle layers was infiltrated with saline and a 2·5 cm circumferential strip of serosa and longitudinal muscle was excised. The cut edges were apposed with interrupted 4/0 chromic catgut sutures to create a flap valve of ileal mucosa with a central core of circular, constricting muscle. The ileo–anal anastomosis was constructed as described for group 1.

4. Ileo–anal anastomosis and J pouch (n = 9). After proctocolectomy, a duplicated J pouch[18] was constructed from the terminal ileum. Two 10 cm lengths of ileum were anastomosed side-to-side with chromic catgut and Vicryl® (Ethicon Ltd.). The distal end of the pouch was left open to accommodate the head of the stapling device which was inserted through the anal stump as described above.

All operations were performed by one surgeon. No defunctioning ileostomy was used. The distance of the anastomosis above the anal verge was measured with a cylindrical rule.

The compliance of the rectal substitute was measured in each animal before the anastomosis was made. A latex balloon, 10 cm in length, was attached to a probe (Gaeltec, Isle of Skye, UK) which incorporated a perfusion channel. The latex balloon was inflated with an infusion of water warmed to 37°C at a rate of 60 ml/min. The pressure within the balloon was determined by a microtransducer and recorded on a Motility Digitrapper® (Synectics Medical, Enfield, UK) for later analysis on an IBM computer (Rochester, USA). A Gaeltec probe without a perfusion channel was left in the anal canal with the microtransducer positioned at the point of maximum resting anal pressure as determined by the station pull-through technique. This remained *in situ* for the duration of the operation apart from the time when the anastomotic gun was inserted. The median value recorded in each animal in the period before the anastomotic gun was inserted was compared with the median value recorded after the stapling device had been removed.

At the end of the operation the peritoneal cavity was lavaged with tetracycline solution. For 3 days thereafter, the animals were restricted to a liquid diet after which they returned to their normal diet (Diet A, Special Diet Services, Witham, Essex) with water *ad libitum*. No medication was administered to reduce the frequency of bowel action.

Assessment after operation

Body-weight. Each animal was weighed after an overnight fast on the morning of the same day each week, and its general health noted.

Manometric studies. These were carried out at 4, 8, 12, 16 and 20 weeks after operation, to determine the compliance and capacity of the 'neorectum' and the pressure profile of the anal sphincter. No bowel preparation was used, but the studies were only performed after the animal had evacuated the neorectum. All manometric studies performed after operation were carried out without sedation, but with the animal supported gently in a sling.

Compliance. The compliance of the neorectum was measured with a latex balloon, 10 cm in length, attached to a Gaeltec probe with a central perfusion channel. The probe incorporated four microtransducers located at 5 cm intervals from the tip. The probe with its attached balloon was inserted through the anal canal which had been generously lubricated with KY Jelly (Johnson and Johnson, Slough,

Table 1 *Postoperative weight loss, daily faecal fat loss and mean intestinal transit times in each of the four operative groups*

	Ileo–anal anastomosis	Ileo–anal anastomosis + myectomy	Ileo–anal anastomosis + myectomy + valve	Ileo–anal anastomosis + J pouch
Maximum weight loss after operation, %	8·7 (5·0–12·8)	11·8 (7·4–15·9)	4·9 (3·4–7·6)	20·2* (12·2–26·1)
Faecal fat loss, g/day	5·6* (5·0–6·6)	3·0 (2·3–3·5)	3·4 (2·9–3·9)	4·0 (3·4–4·3)
Intestinal transit time, h	5·2† (2·6–8·2)	10·5 (9·6–13·9)	12·9 (10·5–14·5)	11·0 (8·4–13·0)

Values are median (interquartile range). * $P<0{\cdot}01$, † $P<0{\cdot}05$

Table 2 *Compliance of the rectal substitute measured during operation and 12 weeks later*

	Ileo–anal anastomosis	Ileo–anal anastomosis + myectomy	Ileo–anal anastomosis + myectomy + valve	Ileo–anal anastomosis + J pouch
During operation, ml/mmHg	0·64* (0·49–0·78)	1·65 (1·16–1·93)	1·51 (0·89–1·68)	1·28 (0·99–1·49)
12 weeks after operation, ml/mmHg	0·8* (0·65–1·0)	1·8 (1·4–2·6)	1·7 (1·3–3·1)	1·53 (0·85–2·6)

Values are median (interquartile range). * Ileo–anal anastomosis *versus* each of the other groups, $P<0{\cdot}01$

UK). One microtransducer was positioned to measure the pressure inside the balloon in the neorectum, another to record pressure in the anal canal, while the remaining two microtransducers were redundant. The balloon was inflated by infusing water at 37°C at a constant rate of 60 ml/min. The pressures recorded were stored on a microchip in a portable electronic collecting device for later computer analysis. The compliance was determined by the reciprocal of the gradient of the pressure–volume curve (ml/mmHg) after correction for the compliance characteristics of the balloon in air.

Capacity. The capacity of the neorectum was measured by infusion of air into a similar latex balloon. The maximum tolerated volume was taken to be the volume at which the animal adopted a defaecatory posture and tried to expel the balloon.

The frequency of bowel action. This was determined at 4-weekly intervals for 20 weeks by simple, albeit tedious, observation over periods of 24 h. The frequency of bowel action was subdivided in an arbitrary manner into bowel actions at which more than 50 g of stool (wet weight) were passed, and all bowel actions. The posture adopted for defaecation, and any evidence of pain or difficulty in passing stool, were noted.

Stool analysis. The consistency of the stool was noted during the periods of observation of the bowel frequency. All stool that was passed over a 24 h period was collected at 4, 8, 12, 16 and 20 weeks after operation and the crude wet weight determined. After thorough mixing, a 15–20 g sample was dried at 70°C for 4–5 days to determine the dry weight and hence the water content. A further 15–20 g aliquot was taken for determination of faecal fat by the method of Van de Kamer *et al.*[19].

Blood analysis. Blood was taken at weekly intervals for the first 4 weeks after operation and at 4-weekly intervals thereafter. Haemoglobin concentration, haematocrit, platelet count, white blood cell concentration and the serum concentration of urea, creatinine, electrolytes, albumin, calcium and phosphate were measured by an autoanalyser.

Intestinal transit time. This was measured on four separate occasions. A modification of the marker technique described by Hinton *et al.* was used[20–22]. The animals each received three capsules with a total of 24 radio-opaque markers. Each stool passed thereafter was collected and, the time having been noted, was placed in a plastic bag and radiographed. The collections were continued until all the pellets had been passed. The mean intestinal transit time was calculated by summation of the products of the number of pellets and time divided by the total number of pellets.

Statistical analysis. The grouped data were expressed as median and interquartile range. The non-parametric data in each of the four experimental groups were compared using the Mann–Whitney U test. Results obtained from the same dog were compared using the Wilcoxon matched pair signed rank test[23].

Results

Morbidity and mortality

Mortality in the four groups did not differ significantly. Three animals died from intestinal volvulus and mesenteric infarction (two ileo–anal anastomosis, one ileo–anal anastomosis and myectomy and ileo–ileal valve) more than 12 weeks after operation. Two animals died of pelvic sepsis (one ileo–anal anastomosis and myectomy and ileo–ileal valve, one ileo–anal anastomosis and J pouch at 4 and 6 weeks respectively) and one animal (ileo–anal anastomosis and myectomy) died during the operation as a result of anaesthetic complications.

The recovery after operation of the animals in the ileo–anal anastomosis and J pouch group appeared to be slower than that of the animals in the other three groups; they remained lethargic and disinterested for longer periods. This was reflected by loss of weight which was significantly greater in the ileo–anal anastomosis and J pouch group than in any other group (*Table 1*).

Manometric studies

Compliance. Myectomy of the terminal ileum resulted in a significant increase in compliance as shown by intraoperative assessment (*Table 2*). The increase was not affected by the construction of the ileal valve and was similar to the compliance recorded in the J pouch. This increase in compliance after myectomy, compared with ileo–anal anastomosis alone, was maintained 20 weeks after operation.

Capacity. The capacity of the rectal substitute was significantly less in the ileo–anal anastomosis group than in each of the other three groups, at each of the 4-weekly studies ($P<0{\cdot}01$). Capacity in the ileo–anal anastomosis and myectomy group was as great as in the ileo–anal anastomosis and J pouch group (*Figure 2*).

Resting anal pressure. Median resting anal pressure was 96 mmHg (interquartile range 84–108 mmHg) before the use of the anastomotic gun, but decreased to 60 mmHg (52–72 mmHg) after the anastomosis had been constructed ($P<0{\cdot}001$) (*Figure 3*). No significant decrease in resting anal pressure was

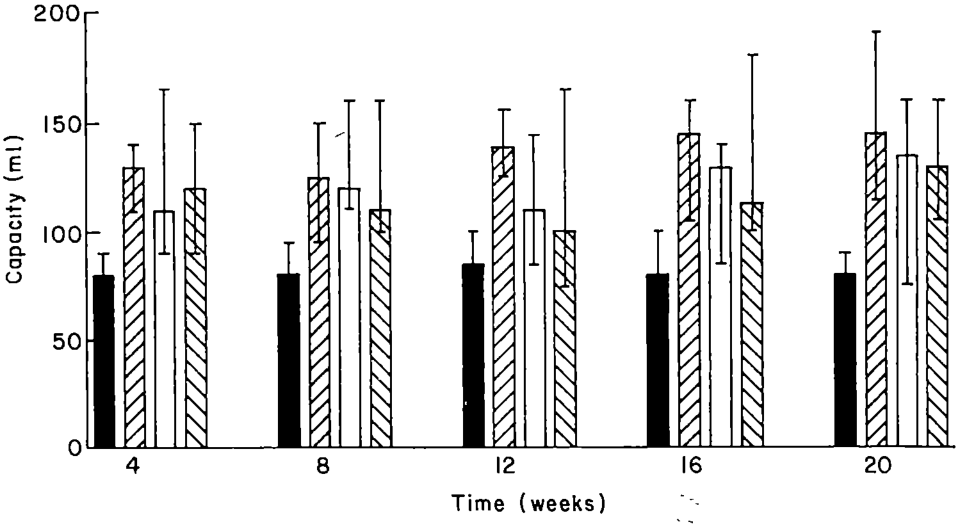

Figure 2 *The capacity of the rectal substitute during the period of the study* ■, *ileo–anal anastomosis,* ▨, *myectomy,* □, *myectomy and valve, and* ▧, *J pouch*

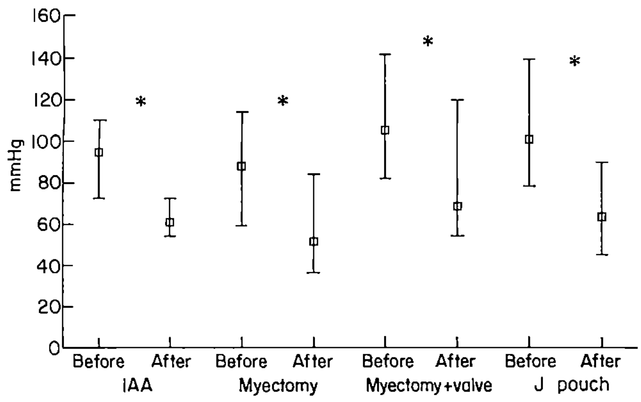

Figure 3 *The maximum resting anal pressure measured during operation before and after the use of the anastomotic gun* (*$P<0.001$) *IAA, ileo–anal anastomosis*

observed in the period before the anastomotic gun was inserted, and the pelvic dissection itself did not lead to a decrease in resting anal pressure, which was 98 mmHg (range 86–108 mmHg) immediately before insertion of the gun. Twenty weeks after operation the median resting anal pressure in each group was: ileo–anal anastomosis, 73 mmHg (62–82 ml); ileo–anal anastomosis and myectomy, 65 mmHg (54–89 mmHg); ileo–anal anastomosis and ileo–ileal valve, 86 mmHg (70–91 mmHg) and ileo–anal anastomosis and J pouch, 84 mmHg (49–97 mmHg) (inter group comparisons, n.s.).

Bowel frequency. The frequency of bowel action was significantly greater in the ileo–anal anastomosis group than in any of the other three groups (*Figure 4*). This was so also when the passage of small (<50 g) amounts of stool was discounted. Bowel frequency in the ileo–anal anastomosis and myectomy and ileo–anal anastomosis and myectomy and ileo–ileal valve groups was similar to that of the ileo–anal anastomosis and J pouch group throughout the study. The animals in the latter group were noted to have difficulty in passing stool and often appeared to be in some discomfort They would adopt a different defaecatory posture, with their backs pressed firmly against the wall. All animals in the ileo–anal anastomosis and myectomy, ileo–anal anastomosis and myectomy and ileo–ileal valve and ileo–anal anastomosis and J pouch operative groups would squat to defaecate and maintained good perianal cleanliness, whereas the animals in the ileo–anal anastomosis group often failed to do so

Stool analysis. The stools passed by the ileo–anal anastomosis animals were more liquid than the stools passed by the animals in the other three groups, whose stools were semi-solid The crude wet stool weight and the dry stool weight were significantly greater in the ileo–anal anastomosis group than each of the other three operative groups. No difference was observed between the stool weights of ileo–anal anastomosis and myectomy, ileo–anal anastomosis and myectomy and ileo–ileal valve and ileo–anal anastomosis and J pouch groups (*Figure 5*). The daily faecal fat loss was also significantly greater in the ileo–anal anastomosis group than in each of the other three operative groups (*Table 1*)

Blood analysis The haematocrit decreased in all animals in the immediate postoperative period but the decrease was not sustained. The white blood cell concentration increased in most animals but this leucocytosis was maintained for longer than 3 weeks only in the two animals who eventually died from pelvic sepsis. No significant differences in blood measurements were found among the four groups of animals.

Intestinal transit. The mean intestinal transit time of each of the four operative groups is shown in *Table 1.* The transit time was significantly less in the ileo–anal anastomosis group than in each of the other three groups. Addition of an ileo–ileal valve did not increase transit time compared with that observed after myectomy alone.

Discussion

The principal findings were that myectomy of the distal ileum in dogs significantly increased its compliance and capacity, slowed intestinal transit and diminished stool weight and the frequency of defaecation Hence, the overall functional results were improved. These changes were maintained throughout the 20-week period of the study. The addition of an artificial ileal valve did not improve the functional outcome compared with myectomy alone. Myectomy of single lumen ileum yielded results similar to those observed after use of the duplicated (J) ileal reservoir.

The idea of myotomy of the ileum is not new. Casanova-Diaz, for example, performed several myotomies of the distal ileum in a patient with familial adenomatous polyposis on whom he performed ileo–anal anastomosis, and reported that the functional result was satisfactory[11] Similar results have been reported after a single 20 cm myotomy[12]. The results of our study support those of Hurst, Imhof and others[13,14] in that myectomy of the ileum significantly increased the capacity and compliance of the rectal substitute and so

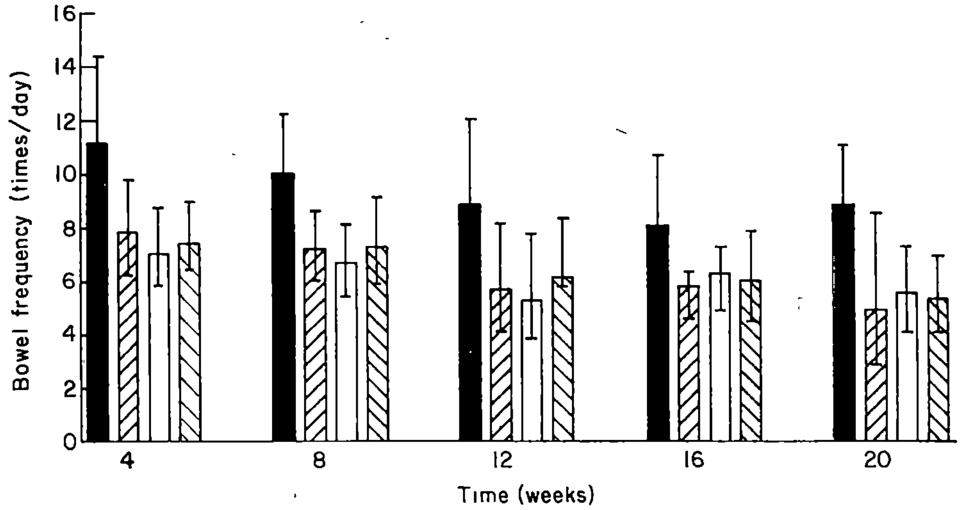

Figure 4 *The frequency of bowel action during the period of the study.* ■, *ileo–anal anastomosis,* ▨, *myectomy,* □, *myectomy and valve, and* ▧, *J pouch*

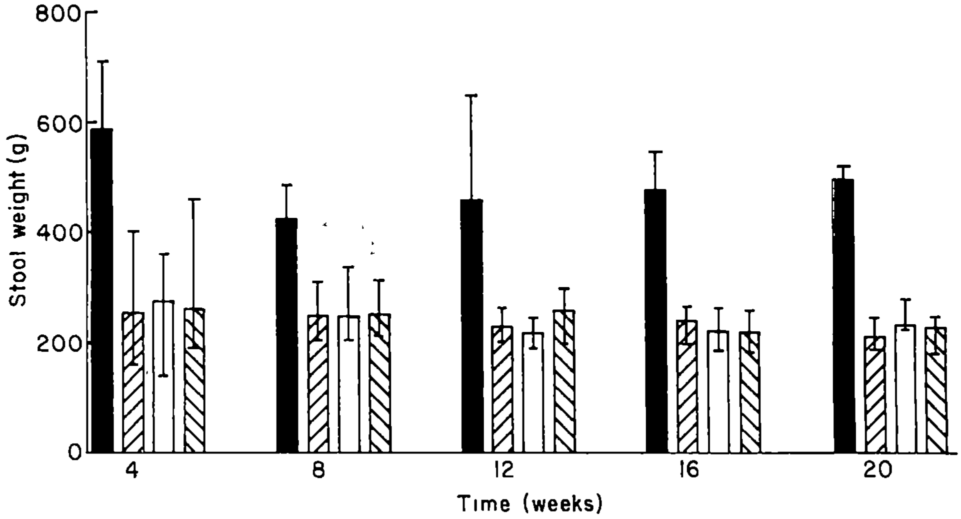

Figure 5 *The stool wet weight during the period of the study* ■, *ileo–anal anastomosis,* ▨, *myectomy,* □, *myectomy and valve; and* ▧, *J pouch*

improved the functional result

The operative mortality in this study, (six of 36 dogs, 17 per cent), was relatively high, but we believe that each of these deaths would have been prevented in man, for example, by the timely use of a defunctioning stoma. No evidence was found of leakage from the myectomy sites or from the suture lines of the J pouch.

The dogs in the J pouch group lost significantly more weight than the other dogs, and took longer to recover from the operation. This degree of weight loss after ileo–anal anastomosis with an ileal reservoir has been remarked upon previously[24].

The dogs tolerated the manometric studies well without need for sedation. Anal sphincter pressure decreased significantly during the operative procedure after the stapling device had been inserted and fired. This could have been due in part to the large diameter (21 mm) of the stapling 'gun' relative to the size of the dog's anus. However, the rectal transection may have been partly responsible for the decrease since resting anal pressure has been found to decrease both after restorative proctocolectomy for colitis[25,26] and after resections for low rectal cancer[27]. Since resting anal pressure is largely a function of the internal anal sphincter, which is a continuation of the muscular coat of the rectum, perhaps loss of excitatory impulses from the rectal muscle after transection accounts for some of the decrease in resting anal pressure. Anal pressures remained reduced throughout the postoperative period, though they were higher after operation than at the end of the operation. Despite the decrease in resting anal pressure, the animals remained continent. During the act of defaecation they adopted the squatting posture which prevents contamination of the coat and they maintained good perianal cleanliness.

The capacities of the rectal substitute in the ileo–anal anastomosis and myectomy, ileo–anal anastomosis and myectomy and ileo–ileal valve and ileo–anal anastomosis and J pouch groups were similar and much greater than in the group that underwent ileo–anal anastomosis alone. The measurement of maximum tolerated volume was found to be reproducible. Although the volume recorded would be influenced by the presence of stool in the ileum at the time of measurement, this potential source of error was minimized by ensuring that the dogs had defaecated before the tests were carried out. The capacity of the rectal substitute did not decrease in the course of the 20-week period of the study. Similarly, the frequency of bowel action and the weight of stool passed did not increase. The benefits of myectomy of the ileum were therefore maintained for at least 20 weeks after operation and so seem likely to be permanent.

The water content, wet stool weight and dry stool weight were each significantly greater in dogs with straight ileo–anal anastomosis than in any of the other three groups. Absorption of water has been previously found to be greater in dogs with lateral isoperistaltic or triplicated reservoirs than in dogs with ileo–anal anastomosis[28]. In man, however, daily stool outputs have been reported to be similar in pouch patients and in patients after straight ileo–anal anastomosis[29]. *In vivo* perfusion techniques in dogs have shown that intestinal adaptation after proctocolectomy is achieved by an increase in the ileal absorption rate[30]. An increase in the intestinal surface area after total colectomy is associated with an increase in the absorptive capacity of ileum[31] and it is possible that the technique of double myectomy allows an increase in intestinal surface area to occur.

Faecal fat loss was also found to be significantly greater after straight ileo–anal anastomosis than in any of the other three groups. Malabsorption of fat has been reported previously after straight ileo–anal anastomosis in man[29] and limited resection of the longitudinal smooth muscle was reported to diminish faecal fat loss after small bowel resection[32]. Alterations in speed of intestinal transit and changes in bacterial flora could help explain such changes in faecal fat excretion.

The technique of myectomy was not difficult. The muscular layer of the ileum is bound loosely to the mucosal layer by the submucous coat through which the smaller blood vessels run. This plane could be easily identified and the strips of seromuscle could be removed without the use of diathermy and with minimal blood loss. In contrast, the dissection of the outer longitudinal layer from the inner circular layer of muscle to create the ileal valve proved to be more difficult, which may be why the addition of an ileal valve did not increase transit time or improve the functional results.

An unsatisfactory clinical outcome in patients who underwent myotomy of the distal ileum with ileo–sigmoid anastomosis was reported recently by Aly and Fonkalsrud[33]. We think that a myotomy incision may heal too quickly, leading to loss of compliance and capacity and to return of high pressure waves[34]. A defunctioning ileostomy is widely used in patients in the course of restorative proctocolectomy and is of obvious value in preventing mortality and decreasing morbidity. However, the addition of an ileostomy might well be counterproductive if myectomy was employed with single lumen ileum because it may be important for the 'neorectum' to be distended regularly by gas and stool. Our preliminary *in vitro* experiments suggested that myectomy produced a greater increase in ileal compliance than myotomy and that two myectomies were superior to a single myectomy. The technique of myectomy of ileum should be feasible in man, as is suggested by Peck's use of ileal grafts to replace rectal mucosa[35]. Although the major problem with such grafts is ischaemia, we found no evidence in this study of ischaemia of the ileum after myectomy.

In conclusion, myectomy of the distal ileum in dogs was found to increase its compliance and capacity and thus to improve the functional results of ileo–anal anastomosis. The functional results after myectomy did not differ significantly from the results obtained by the use of a duplicated J pelvic reservoir. Whilst acknowledging the gulf that exists between the results of these experimental observations and the practical realities of surgery in man, we suggest that a prospective trial of myectomy of single lumen ileum may be indicated as a possible alternative to J, S or W pelvic reservoirs in restorative proctocolectomy in man.

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Elective resection for diverticular disease of the sigmoid colon

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From 1966 to 1987, 177 consecutive patients were operated on electively for diverticular disease of the sigmoid colon. The indications for surgery were: colovesical fistula (n = *12*), *suspicion of residual abscess* (n = *39*), *two or more previous attacks of acute inflammation* (n = *52*), *chronic symptoms* (n = *72*) *and suspicion of carcinoma* (n = *2*). *An abscess was found at operation in 76 patients* (*43 per cent*) *and this was extracolic with local peritonitis in 52 patients* (*29 per cent*). *An unsuspected abscess was found in 25 of the 72 patients operated on for chronic symptoms. Colonic resection with primary anastomosis was performed in 95 per cent of the 177 patients and in 94 per cent of those 52 patients with an extracolic abscess. There were no postoperative deaths and no clinical anastomotic leakages. Long-term results were very good in 85 per cent of the 177 patients and in 82 per cent of the 72 patients operated on for chronic symptoms. The results of this series suggest that a one-stage procedure can be safely performed with some technical precautions in most patients operated on electively for diverticular disease, even if an extracolic abscess is found. The good long-term results in patients operated on for chronic symptoms suggest that such symptoms should be taken into account with respect to surgical indications.*

Keywords: Sigmoid colon, diverticular disease, elective colonic resection

Diverticular disease of the colon has been increasing in frequency, probably as a result of alterations in diet. Emergency procedures for severe complications have been well documented[1]. Indications for elective surgery have never been well defined and elective surgical management has rarely been specifically examined[2,3]. The aim of this study was to evaluate immediate and long-term results of elective resection for sigmoid diverticular disease in 177 consecutive patients.

Patients and methods

From January 1966 to January 1987, 177 patients were operated on electively for complicated sigmoid diverticular disease. Eighty patients were operated on before 1980 and 97 between 1980 and 1987 The same senior surgeon selected patients for surgery and was responsible for follow-up One hundred and sixty-seven patients (94 per cent) were selected for surgery from patients first admitted to other medical units and referred for a potential surgical indication. Only ten patients were originally examined for acute symptoms in the authors' surgical unit and were treated medically for 1–3 months before operation. All operations were performed by a senior and a junior surgeon in the same hospital There were 109 men and 68 women. Mean age was 60 years (range 30–87 years) Patients with coexisting carcinoma and with complicated diverticular disease not located in the sigmoid colon were excluded.

Indications for surgery

Patients were retrospectively classified in four groups according to the indications for elective resection In the first group ($n = 51$) an obvious colovesical fistula was present in 12 patients, and a residual intra-abdominal abscess was suspected in 39 patients in whom a painful mass was palpable in the left lower quadrant or in whom contrast radiography demonstrated a persistent sinus outside the lumen or an extrinsic compression of the sigmoid colon. In this group of patients the mean(s.d.) interval between the attack of inflammation and operation was 3(1) months (range from 15 days to 6 months) In the second group ($n = 52$), patients had two or more previous attacks of acute inflammation including abdominal pain, fever and some degree of colonic obstruction. In this group the mean(s d) interval between last attack of inflammation and operation was 3 5(1 6) months (range 2–6 months) In the third group ($n = 72$), patients complained of chronic symptoms, defined as those persisting for more than 2 years, and including functional colonic disturbance (constipation or diarrhoea) and pain in the left lower abdominal quadrant Some of these patients also had episodes of unexplained bleeding ($n = 10$), dysuria ($n = 18$) and/or radiological or endoscopic stenosis of the sigmoid colon ($n = 8$). These chronic symptoms occurred after one attack of inflammation in 44 patients (61 per cent) and without any previous attack in 28 patients (39 per cent) In the fourth group ($n = 2$), contrast radiography demonstrated a retrograde obstruction simulating a sigmoid carcinoma.

Surgical management

Patients were operated on after a simplified bowel preparation Colonic left flexure mobilization was performed in most cases before dissection of the inflamed sigmoid colon in order to obtain a proper length of healthy colon for anastomosis The entire sigmoid colon was resected in all cases, usually with a posterior rectal mobilization. The resection was normally limited to the sigmoid and extended to the descending colon only when a thickened, obviously inflamed, colonic segment was present Non-inflamed diverticula proximal to the severely diseased area were not resected. A one-stage resection was performed in all patients, except when the lesions extended to the rectum and in patients with advanced age or at high operative risk Colorectal anastomoses were performed with a single layer of interrupted silk sutures In cases of extracolic abscess with local peritonitis, local decontamination with excision of necrotic tissue and antiseptic irrigation was performed The omentum, pedicled when necessary, and/or the mobilized caecum were used to separate the anastomosis from the inflamed peritoneum and to obliterate a persistent pelvic dead space The intestinal loops were carefully arranged in the peritoneal cavity and the abdominal wall was closed without drainage

Follow-up

All patients were reviewed, or answered a questionnaire, about postoperative bowel habit and additional episodes of abdominal pain. Mean follow-up was 5·8 years (range 2–22 years).

Results

Operative findings

As expected after preoperative examination, 12 patients had a colovesical fistula An abscess was present in 76 patients (43 per cent). In 24 patients, the abscess was wholly contained within the mesentery or the bowel without local peritonitis, or was a small pericolic lesion. In 52 patients, the abscess was extracolic with local peritonitis; it was more than 5 cm in

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Table 1 *Correlation between operative findings in 165 patients operated on electively for sigmoid diverticular disease and preoperative symptoms (patients with colovesical fistula are not considered)*

	Operative finding		
	Abscess	Inflamed diverticulitis	Diverticulosis
Group I (*n*=39)	30 (77)	9 (23)	0
Group II (*n*=52)	20 (38)	23 (44)	9 (17)
Group III (*n*=72)	25 (35)	37 (51)	10 (14)
Group IV (*n*=2)	1	1	0

Values in parentheses are percentages. Group I, suspicion of residual intra-abdominal abscess, group II, two or more attacks of acute inflammation, group III, chronic symptoms; group IV, inability to exclude a carcinoma

Table 2 *Correlation between operative procedure and operative findings in 177 patients operated on electively for diverticular disease*

	Operative procedure	
Operative finding	Resection with anastomosis (*n*=169)	Hartmann's procedure (*n*=8)
Colovesical fistula	10	2
Abscess		
Within the mesentery	21*	3
Extracolic	49	3
Inflamed diverticulitis	70	0
Diverticulosis	19	0

* One patient had a covering colostomy

diameter and full of pus and faeces in 12 patients and less than 5 cm in 40 patients. The sigmoid diverticular disease was inflamed in 70 patients (40 per cent) and uncomplicated in 19 (11 per cent). Operative findings were correlated with preoperative symptoms (*Table 1*). An abscess was found in 25 (35 per cent) of the 72 patients operated on for chronic symptoms, 11 of whom did not have any previous attack of fever. Diverticular disease was uncomplicated in nine of the 52 patients operated on for attacks of inflammation.

Operative procedure

Primary resection and anastomosis were performed in 169 patients (95 per cent), with a covering colostomy in one. Hartmann's procedure was performed in eight patients with extension of the lesions to the rectum or at high operative risk. Surgical procedures were correlated with operative findings (*Table 2*). A one-stage procedure was performed in 49 (94 per cent) of the 52 patients with an extracolic abscess.

Postoperative course

There were no postoperative deaths. Postoperative complications occurred in ten patients (5·6 per cent). These were minor in six patients, including wound infection (*n*=2) and haematoma (*n*=1). Major complications, requiring reintervention, occurred in four patients: one pelvic abscess without an obvious leak, one small bowel obstruction, one gastric distension related to an obstruction of the duodenojejunal flexure and one perforation of the gallbladder. There were no obvious anastomotic leakages. Latent leakages were not radiologically investigated.

Long-term results

Continuity was restored in three of the eight patients with a Hartmann's procedure A permanent stoma was left in five elderly patients. Long-term results were very good in 151 patients (85 per cent) who had no further symptoms. Twenty patients (11 per cent) complained of persistent pain or intestinal dysfunction. Recurrent attacks of pain or fever occurred in six (3 per cent), and were attributed (without direct proof) to recurrent inflammation of diverticular disease. Reintervention was not necessary in any case The late deaths of 15 patients were not related to complications of diverticular disease. Long-term results were correlated with operative indications (*Table 3*) and these were good in 82 per cent of those operated on for chronic symptoms.

Discussion

This is a large series of elective operations with long follow-up. The results suggest some comment on technical management and indications for elective surgery for sigmoid diverticular disease. The operative mortality rate was nil and the postoperative morbidity rate was very low There were no anastomotic leakages despite a high rate of one-stage resections with anastomosis, even in patients with an extracolic abscess. This one-stage policy in the management of diverticular disease complicated by an extracolic abscess is unusual[2,4–7]. The only local contraindication in this series for a one-stage resection was the presence of important lesions of the rectal wall above and below the peritoneum or high operative risk. Nevertheless, the results compare favourably with those of other series in which the data for emergency and elective surgery were combined[4–6,8,9]. Technical safety measures in cases of pelvic abscess may account for this Firstly, the anastomosis was performed with margins of resection free of inflammation, without any tension (the left flexure was mobilized in most of the patients), and was kept apart from the inflamed peritoneum. Secondly, care was taken to ensure that no dead space persisted in the pelvis. The usefulness of the omentum and the caecum for this purpose must be emphasized. Omentum, pedicled on the left gastroepiploic artery when necessary[10], was brought down behind the small intestine and beside the descending colon into the pelvic space, in order to cover the inflamed pelvic wall and to fill the residual peritoneal cavity. This omentum kept the anastomosis away from the inflamed peritoneum and facilitated healing. The caecum, mobilized if necessary, was also used often to fill the residual dead space and was placed in front of the anastomotic area. With these precautions the anastomosis did not need the protection of a temporary transverse colostomy. Abdominal drainage was considered useless and was never used. It has been demonstrated recently that prophylactic drainage after colonic anastomosis has no advantage[11] and the results of this series suggest that, with the precautions described above, routine drainage can be omitted. This policy has allowed a significant reduction in staged procedures in elective surgery. It has the important advantage

Table 3 *Correlation between long-term results in 177 patients operated on electively for sigmoid diverticular disease and preoperative symptoms*

	Long-term results		
	No complaint	Persistent pain and/or intestinal dysfunction	Recurrent attacks of fever
Group I (*n*=51)	47 (92)	2 (4)	2 (4)
Group II (*n*=52)	43 (83)	6 (12)	3 (6)
Group III (*n*=72)	59 (82)	12 (17)	1 (1)
Group IV (*n*=2)	2 (100)	0	0
Total	151 (85)	20 (11)	6 (3)

Values in parentheses are percentages Group I, suspicion of residual intra-abdominal abscess, group II, two or more attacks of acute inflammation; group III, chronic symptoms; group IV, inability to exclude a carcinoma of reducing hospital stay, the period of disability and, ultimately, the cost of care.

Long-term results were satisfactory in the present series which suggests two things. Firstly, patients with chronic pain in the left lower quadrant and functional colonic disturbance for more than 2 years, even without any previous clinically acute attack of inflammation, should be considered for elective surgical resection. Secondly, diverticula located above the diseased area do not require a more extended colonic resection. In most reports elective surgery for diverticular disease was considered in patients with signs of persistent abscess or fistula and/or with recurrent attacks of local inflammation[12]. Seventy-two (41 per cent) of our patients were operated on for symptoms persisting for more than 2 years. These symptoms occurred without any previous attack of fever in 28 (39 per cent) patients. The excellent results obtained in 82 per cent after resection of the pathological sigmoid strongly suggest, although criteria for operation were not prospectively defined, that chronic symptoms should be part of the indications for elective surgery in diverticular disease. The finding of an unsuspected abscess in 35 per cent of patients operated on for chronic symptoms supports this policy. However, the proportion of unsatisfactory results (18 per cent) in this group was higher than in the other groups. Irritable bowel syndrome associated with diverticular disease was probably the main cause of failure. Patients with concomitant psychological disorder should also be carefully assessed The long-term results were satisfactory despite a non-aggressive policy in terms of length of colonic resection. When distant diverticula were present proximal to the severely diseased area, resection was not extended. In all cases, the whole sigmoid was resected and anastomosis was performed with the rectal segment. Recurrent attacks of pain and fever were observed in only six patients in the whole series. These could not be attributed with certainty to recurrent inflammation of diverticular disease and they resolved spontaneously. These results correlate well with those of Benn *et al.*[13].

One-stage elective surgery can be performed in complicated diverticular disease of the sigmoid colon without mortality, with a low morbidity rate and with a short period of disability. In cases of local septic complications of diverticular disease, surgical treatment should be performed electively. A correct selection of patients with chronic symptoms is necessary to obtain good long-term results. More patients with chronic symptoms of diverticular disease could be cured by elective surgical treatment.

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Gracilis muscle transposition for faecal incontinence

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Transposition of the gracilis muscle for faecal incontinence was performed in 13 patients. Six gained satisfactory continence, four were improved, two did not benefit from the operation and one patient died from intercurrent disease before closure of a pre-existing colostomy. Anal manometry compared with a control group showed no alteration in resting anal pressure at a median of 35 mmHg (range 5–63 mmHg), whereas maximum squeeze pressure increased from a median of 38 mmHg (range 5–79 mmHg) to 59 mmHg (range 10–143 mmHg) (P = 0·041) which was, however, significantly lower than 130 mmHg (range 81–236 mmHg) in the control group. All patients who benefited from the operation had an increase in maximum squeeze pressure. The ability to retain a viscous fluid in the rectum was measured in seven patients, four of whom had gained satisfactory continence and three of whom had improved continence. They were able to retain a median volume of 200 ml (range 50–225 ml) without leakage compared with 325 ml (range 250–400 ml) in the control group. These patients could retain the maximum amount of viscous fluid for 5–8 min, whereas all control subjects could do so for more than 15 min. It is concluded that, although gracilis transposition never results in normal continence, acceptable continence may be achieved in selected patients provided careful attention is paid to the technical details of the procedure and provided that systematic postoperative exercises are performed.

Keywords: Anal incontinence, anal atresia, gracilis transposition

Transposition of the gracilis muscle for anal incontinence was described by Pickrell *et al.* in 1952[1]. Since then the results of this technique have been described in a few case reports, but larger patient series are sparse. The clinical results obtained in these series have, however, been rather conflicting[2,3]. We describe here the results of gracilis transposition for anal incontinence in 13 patients.

Patients and methods

Thirteen patients, 12 women and one man, median age 44 years (range 18–55 years) underwent gracilis muscle transposition For comparison of anorectal parameters, 12 healthy women, median age 45 years (range 25–75 years), served as controls.

The indications for gracilis transposition are shown in *Table 1*. The patients with traumatic or idiopathic incontinence had all had an unsuccessful sphincter reconstruction or postanal repair before the gracilis operation. Two patients were incontinent due to neurological disease (one sacral meningocele and one slipped disc) without involvement of the muscles of the legs. One patient had a damaged anal sphincter following irradiation of a cancer of the uterus, and two adults (aged 18 and 23 years) were incontinent due to anal atresia despite an anal reconstruction in childhood.

Anal canal pressures were measured with an open-ended perfused system consisting of three rigid, low compliance polyvinyl catheters with an outer diameter of 2 mm and an inner diameter of 1 mm; each catheter ended in a steel cap with the same dimensions and three side-holes radiating at 120°. Each catheter was perfused with a flow rate of 0·7 ml/min through a water-filled strain gauge connected to a four-channel ink recorder. The manometric system had a pressure/time of 800 mmHg/s

Before operation the patients were instructed by physiotherapists in the exercises of the transposed gracilis muscle they were to perform after surgery Mechanical bowel cleansing was achieved by oral administration of an electrolyte solution, and antibiotic prophylaxis with gentamicin 80 mg and metronidazole 500 mg was given three times daily for 3 days, the first dose being administered during induction of anaesthesia. The patient with radiation damage of the sphincter already had a colostomy on admission but otherwise protective colostomies were not used.

Differences in anal pressures and rectal volumes were assessed by the Mann–Whitney *U* test.

Operative procedure

The operation was performed essentially as described by Pickrell *et al.*[4]. One long incision was made in the thigh and one short oblique incision was made over the medial condyle of the tibia where the tendon of the gracilis muscle enters the pes anserinus The importance of dividing the tendon close to its insertion to the bone is emphasized. After mobilization of the muscle and careful dissection of the neurovascular bundle, the muscle was drawn clockwise around the anal canal through right and left lateral perianal incisions. These incisions were chosen to preserve the anterior and posterior raphes through which the muscle and its tendon were positioned. Finally, before the tendon was sutured to the opposite ischial tuberosity with non-absorbable sutures, the thigh was adducted to its normal position to ensure tight closure of the anal canal in this position.

After operation the patients had a liquid diet and opiates for 5 days and were confined to bed with the leg adducted for 10 days. Exercises were started 14 days after operation and were continued after discharge under supervision of specially trained physiotherapists.

Results

Two patients developed minor infections in the perianal wounds; in one patient this required surgical drainage which was followed by an uneventful recovery.

Table 1 *Indications for transposition of the gracilis muscle in patients with anal incontinence*

Indications for surgery	No. of cases
Traumatic incontinence:	
Obstetric injury	2
Surgical trauma	2
Idiopathic incontinence	4
Neurological disease	2
Radiation damage	1
Anal atresia	2

The patients were followed for 4–37 months after the operation, median 14 months. Six patients gained satisfactory continence, i.e. they were able to contain both solid and soft faeces, suppress defaecation sufficiently long to reach a toilet, and never wore pads. Four patients were continent only for solid faeces and wore pads intermittently. Maximum continence was achieved after a median of 5 months (range 2–9 months). Two patients remained as incontinent as before the operation One of these later had a successful artificial anal sphincter implantation[5,6]. The patient who had a pre-existing colostomy was lost to follow-up, having died from intercurrent disease 3 months after the gracilis transposition and before the colostomy could be closed. One patient had difficult faecal evacuation and needed dilatation 4 months after surgery. Following this she had only minor problems with evacuation when she raised the buttocks a little from the toilet and kept her thighs adducted.

Median resting anal pressure in the patients before operation was 34 mmHg (range 0–75 mmHg) compared with 67 mmHg (range 52–119 mmHg) in the control group ($P=0\cdot0025$). Maximum squeeze pressures were 38 mmHg (range 5–79 mmHg) and 130 mmHg (range 81–236 mmHg) respectively ($P=0\cdot001$). All patients had normal rectal sensation and a maximum urge to defaecate at a median volume of 130 ml compared with 210 ml in the control group ($P=0\cdot16$)

Postoperative laboratory investigations showed a median resting anal pressure of 35 mmHg (range 5–63 mmHg) which did not differ significantly from the preoperative value. There was no correlation between the change in resting anal pressure and the clinical result. Median squeeze pressure was 59 mmHg (range 10–143 mmHg) which was significantly higher than before operation ($P=0\cdot041$). In six patients squeeze pressure was unchanged or decreased and in six it was increased. All patients who gained satisfactory continence had increased squeeze pressures. Median maximum tolerable rectal volume was 140 ml which did not differ from the preoperative value.

The ability to retain a viscous fluid in the rectum was measured in seven patients (four of whom had gained satisfactory continence and three improved continence). These patients were able to retain 200 ml (range 50–225 ml) without leakage compared with 325 ml (range 250–400 ml) in the control group ($P=0\cdot005$). The patients could retain the maximum amount of viscous fluid for 5–8 min whereas all control subjects could do so for more than 15 min.

Discussion

Results of gracilis transposition for anal incontinence have been conflicting. Pickrell *et al*[4] described satisfactory results in 18 children and 16 adults, but did not give any details concerning degree of continence and follow-up Corman[2] has reported the results of gracilis transposition in 13 adult patients with a follow-up of 3–48 months The results, although slightly better, are similar to those of the present series

Recently Yoshioka and Keighley[3] reported extremely poor results in a series of six patients, none of whom benefited from the operation Five of their six patients suffered severe postoperative sepsis and one must, therefore, suspect that sepsis was at least partly responsible for their poor results. Autologous transposition of a well vascularized muscle does not carry any greak risk of infection. Neither in the patients described here nor those in Corman's series was infection a significant problem. It seems, therefore, that a meticulous surgical technique with painstaking dissection and preservation of the vascular supply of the transposed muscle obviates ischaemic necrosis and the infection that ensues.

Another important technical detail is adduction of the leg before suturing the gracilis tendon to the ischial tuberosity We were not aware of this in two patients who were subsequently only able to tighten the muscle around the anal canal by extreme abduction of the thigh; both patients had poor results.

Postoperative training under professional surveillance is important and should be continued for several months; in some patients the maximum effect is only obtained after months of exercising. As with other kinds of surgery for anal incontinence, regulation of bowel habit is mandatory for a successful outcome. Patients with chronic diarrhoea will almost never obtain a satisfactory result no matter what kind of surgery is performed.

Gracilis transposition will not result in 'normal' control of defaecation, since striated muscle is unable to maintain contraction for a prolonged period of time. In the patients who were examined for their ability to retain viscous fluid, 9 min was the longest duration of maximum contraction. This problem may be overcome by implantation of a neuromuscular stimulator, as recently described experimentally in dogs[7] and in a single patient[8].

Furthermore, patients often have to perform some rather awkward manipulations of their thighs to contract the muscle, some find adduction against resistance most effective while others find that forceful abduction, which simply tightens the muscle, is preferable. After some months patients may develop a conditioned reflex whereby they manage to contract the muscle in response to an urge to defaecate without consciously manipulating the thigh This results in a suppression of the defaecation urge similar to that in normal individuals[8].

In conclusion, gracilis transposition, although not applicable in all cases of anal incontinence where local procedures on the anal sphincters have failed, should be considered in selected patients Acceptable faecal control may be obtained.

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Survey of the use of thrombolysis for acute limb ischaemia in the UK and Ireland

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A total of 156 vascular surgeons from the UK and Ireland responded to a postal questionnaire on the use of thrombolysis in acute limb ischaemia. Almost half had used thrombolysis in the previous 12 months. Low dose intra-arterial streptokinase (89 per cent) was the regimen most frequently used, but 33 per cent had used intravenous streptokinase. Detailed results for 103 patients (limb salvage rate 60 per cent, amputation rate 35 per cent, mortality rate 5 per cent) were similar to those of previously published reports. Complications in most series were infrequent, but in the entire survey there were six bleeding-related deaths and one death from anaphylaxis. A total of 67 per cent of surgeons with working experience indicated that selected patients with acute arterial thromboses were most suitable for thrombolysis, particularly if there was no neurological deficit and no run-off for surgical bypass. Distal or late emboli and graft occlusions were regarded as appropriate by some surgeons. This study demonstrated that many vascular surgeons currently use thrombolysis, although sparingly and in selected cases. Patients with acute limb ischaemia should be managed by experienced vascular surgeons who are aware of the new therapeutic alternatives, an ideal supported by almost three-quarters of respondents to this survey.

Keywords: Thromboembolism, fibrinolysis, streptokinase, tissue plasminogen activator

Streptokinase was discovered by Tillett and Garner in 1933[1] Its use was initially investigated in acute limb ischaemia in the 1960s when intravenous infusions were used The results were disappointing with only about 30 per cent of patients deriving benefit, and haemorrhage was commonly reported[2,3]. In 1974, Dotter proposed the use of low dose intra-arterial infusions of streptokinase for acute limb ischaemia[4], a technique that seems to improve clinical results and reduce bleeding complications. Many publications have reported improvement in about two-thirds of patients treated[5–7]. Enthusiasts have proposed that thrombolysis merits a place in the management of acute limb ischaemia, yet there have been no controlled trials and only a handful of randomized studies exist Some surgeons therefore remain sceptical of the benefits of the technique. This survey was done to identify the extent of the use of thrombolysis in the UK and Ireland and to try to obtain a consensus by which patients should be treated.

Methods

A total of 275 surgeons with an interest in vascular surgery (the membership of the Vascular Surgical Society of Great Britain and Ireland) were circulated with a questionnaire requesting details of their use of thrombolysis for acute limb ischaemia in the previous year, with results if available The surgeons were also asked for their opinions on the role and indications for thrombolysis for this condition.

Results

A total of 156 surgeons replied (57 per cent of the Society's membership). Seventy (45 per cent) had used thrombolysis in the previous year. Low dose intra-arterial streptokinase was used as the main regimen by 89 per cent of these surgeons (*Table 1*), but was the sole method for only 56 per cent. Many surgeons used a variety of agents and methods. The majority of respondents treated only a handful of patients; only four centres had used thrombolysis on more than ten occasions in the 12 months. A total of 26 surgeons provided detailed results of 103 patients: limb salvage rate 60 per cent, amputation rate 35 per cent and mortality rate 5 per cent Of the remaining 44 surgeons, 42 per cent reported limb salvage rates in excess of 50 per cent.

Details of complications were recorded by 58 respondents. Almost one-quarter reported trouble-free thrombolysis. Minor haemorrhage at the groin puncture site (50 per cent) was the most frequently stated complication, but 26 per cent of respondents reported major haemorrhage requiring blood transfusion, and 33 per cent reported catheter problems, usually pericatheter thrombosis. However, the actual incidence of these problems was low, complications rarely being recorded in more than half the patients treated by any centre. In the survey overall, seven deaths were reported due to thrombolytic therapy. There were five deaths from haemorrhage after intra-arterial streptokinase, and one non-fatal stroke. One patient died from anaphylaxis and one from haemorrhage after intravenous streptokinase.

Surgeons with experience of thrombolysis were considerably more enthusiastic about its use than the others, although it was noteworthy that almost one-third of experienced surgeons felt unable to offer an opinion on the optimal patients for treatment in each category (*Table 2*). The main indication for thrombolysis, agreed by 67 per cent of experienced surgeons,

Table 1 *Methods of thrombolysis used for acute limb ischaemia by 70 surgeons in the UK and Ireland*

	%
Low dose intra-arterial streptokinase	89
Intravenous streptokinase	33
Intra-arterial tissue plasminogen activator	8
Intra-arterial urokinase	4
Intraoperative streptokinase	1

Table 2 *Response to the question 'In which cases of acute limb ischaemia is there a role for thrombolysis?'*

	Agree	Disagree	Don't know
All limbs	9 (5)	63 (49)	28 (46)
All emboli	4 (3)	66 (47)	30 (50)
All thromboses	16 (11)	51 (40)	33 (49)
Graft occlusions	43 (30)	26 (24)	31 (46)
Selected emboli	46 (35)	24 (17)	30 (48)
Selected thromboses	67 (50)	2 (5)	31 (45)

Figures represent the percentage of surgeons responding with experience of thrombolysis ($n = 70$); those in parentheses are the percentages of the whole population surveyed ($n = 156$)

was recent arterial thrombosis (in selected cases). In particular, patients with acute-on-chronic thrombosis, short duration of symptoms, non-reconstructable problems, distal occlusions, poor run-off, high operative risk and no neurological deficit were mentioned as the most appropriate cases. Thrombosed popliteal aneurysms and thromboses occurring after angioplasty were also singled out as suitable.

Selected emboli were suggested as suitable by 46 per cent of experienced surgeons, particularly in patients least likely to benefit from embolectomy, such as those with distal or late emboli. Also mentioned were patients with continued ischaemia after a failed embolectomy. A total of 43 per cent also thought that patients with acute graft thromboses would benefit, although knitted Dacron® (E.I. du Pont de Nemours and Company, Wilmington, Delaware, USA) grafts and those recently inserted were not suitable. Vein and polytetrafluoroethylene grafts in particular were recommended for thrombolytic treatment.

Many respondents registered enthusiasm for thrombolysis and ten centres indicated they were involved in research in this area. A total of 74 per cent of respondents thought that ideally all patients with acute arterial ischaemia should be managed by a surgeon with expertise in vascular surgery.

Discussion

Thrombolysis is now established as a therapeutic alternative in the management of selected cases of acute limb ischaemia, although its exact role is not yet known[8–11]. This survey has shown that almost half of the vascular surgeons who replied had used the technique in the previous 12 months. Although this may be an overestimate if non-responders are non-users, it demonstrates how widely used thrombolysis has become in a short space of time.

Although low dose intra-arterial streptokinase was the method of choice in most centres, it was noteworthy that intravenous streptokinase is also commonly used, probably due to its ease of administration. The results and complications of intra-arterial streptokinase parallel those in previously published reports and confirm that useful clinical benefits can be achieved, although it must be emphasized that there remains a small but significant mortality from bleeding even though a low dose is used. One criticism is the wide variety of methods that have been used. There is good evidence that reductions in complications such as pericatheter thrombosis can be achieved by adherence to a standard protocol[7] These clinical benefits were achieved despite the small numbers treated in each centre and are in contrast to a previous survey where the success rate was proportional to the overall thrombolytic experience of each clinician[12].

Selected cases of acute thrombosis were thought most suitable for thrombolysis, especially those least likely to have a good outcome from surgery. Fewer surgeons recommended thrombolysis for emboli, partly because the results of surgical embolectomy are better but also because of a theoretical risk of further embolism from a cardiac source[3,13] In reality, results for emboli may be superior to those of thromboses[14]. Thrombolysis for graft occlusion is a difficult subject because published results vary from poor[15] to excellent[16]. Almost half of the experienced surgeons saw a role for thrombolysis in graft occlusions and further study in this area would be helpful.

It is clear that thrombolytic therapy is a fast-expanding method of treatment, although it is used selectively and sparingly by most surgeons. It is encouraging that several centres are actively engaged in thrombolysis research. However, the patients with acute limb ischaemia are few and varied and it may be sensible if research effort was pooled and co-ordinated so that multicentre studies could be performed to assess the exact roles of surgery and thrombolysis and to compare new agents.

Now that thrombolysis is agreed as an option in the management of patients with acute limb ischaemia, it is time that the management of the condition ceased to be every general surgeon's business[17]. Patients with acute limb ischaemia should be managed by surgeons with vascular experience who are aware of, and have access to, the new therapeutic alternatives, an ideal supported by almost three-quarters of respondents to this survey. Indeed referral of patients to centres with vascular expertise can be shown to yield improved results[18]. This finding has not inconsiderable implications in terms of staffing and resources, but could in the long run yield real benefits in limb salvage after acute limb ischaemia.

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Resympathectomy of the upper extremity

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Resympathectomy was performed in 27 patients (eight bilaterally) with ischaemic hand phenomena. An extended operative technique, resecting parts of the second and third intercostal nerves and their surrounding tissue, was used. In all 35 procedures the posterior extrapleural approach was used. Follow-up was from 3 to 12 years. Only the sympathetic ganglia had been removed during the previous surgery by the axillary approach (67 per cent of these patients had had a transient response for between 6 months and 2 years; 33 per cent had had no response at all). A direct subjective improvement was seen after 27 of the 35 reoperations (77 per cent). In 14 patients continuous wave Doppler ultrasound studies were available and showed a significant increase in peak forward frequency after operation ($P < 0{\cdot}001$)*. From these data it may be concluded that it is possible to obtain a resympathectomy effect, but reoperation should be reserved for special cases for whom survival of digits is essential.*

Keywords: Resympathectomy, ischaemic hand phenomena

The high proportion of recurrence of ischaemic symptoms after thoracic sympathectomy is an unsolved problem. Operative procedures have been modified several times. Most procedures have good results immediately after operation but recurrent symptoms are frequent. Many explanations for these failures have been given. The anatomical variation in the sympathetic chain is one of the most important explanations[1–3]. The intrathoracic nerve of Kuntz[4] via which sympathetic nerve fibres reach the brachial plexus without passing through the sympathetic trunk may be relevant in such failures. Kirgis and Kuntz[5] in 1942 described a similar nerve bundle connecting the second and third intercostal nerves.

Regeneration of preganglionic fibres is another explanation for the return of vasospasm after sympathectomy for Raynaud's disease[2,6–10]. The fact that autonomic nerve fibres regenerate in animals lends credence to this point of view[11,12]. In patients in whom the sympathetic tone in the blood vessels of the hand returns, or a residual sympathetic tone appears to persist, resympathectomy seems a logical consideration. This is especially so in patients in whom previous operation has removed only sympathetic ganglia without resecting the second and third intercostal nerves and surrounding tissue.

In 1982 Lemmens[13] described the possibility of a resympathectomy in such patients using his thoracodorsal sympathectomy. By resecting the second and third intercostal nerves and surrounding tissue *en bloc* he was able to achieve a resympathectomy effect.

Patients and methods

Twenty-seven patients presented from other hospitals after an upper thoracic sympathectomy In all patients only the sympathetic ganglia had been removed by an axillary approach, 67 per cent of the patients had had a transient response for between 6 months and 2 years. The other 33 per cent had had no response at all

All patients underwent resympathectomy by the posterior extrapleural approach. The second and third intercostal nerves with their spinal ganglion and surrounding tissue were removed (*Figure 1*) The high thoracic sympathetic ganglia had been resected in all patients in the prior operation and were not found at reoperation In the 27 patients 35 sides were operated on. They could be divided into four groups related to the clinical diagnosis. In this study the classification and nomenclature of Lemmens[14] has been used

Primary Raynaud's phenomenon

This disease is characterized by a symmetrical 'painless' triphasic discoloration of the hands and fingers, in which no underlying disease can be found.

Fifteen patients (14 women, one man) were classified as having primary Raynaud's phenomenon and 22 sides were operated on. The mean age in this group was 38 years (range 22–51 years). In none of the patients could any underlying disease be detected, either by physical examination or laboratory data All laboratory data (Rose, latex test, lupus erythematosus factor) were normal and investigation for cryoglobulin and agglutinin was negative.

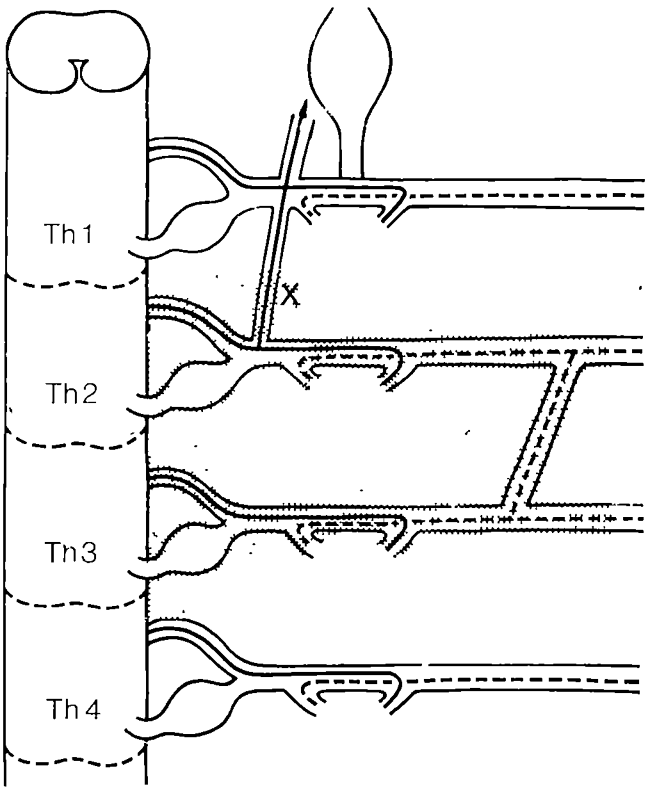

Figure 1 *Schematic representation of the upper thoracic chain in relation to the spinal nervous system after resection of the sympathetic ganglia only (posterior view). X, intrathoracic nerve described by Kuntz, □, second and third intercostal nerves with their spinal ganglion and surrounding tissue which are removed at resympathectomy*

Table 1 *Increase in peak flow frequency in radial and ulnar arteries after resympathectomy in 14 patients*

	Operated side			Non-operated side		
	Before	After	*P*	Before	After	*P*
Radial peak flow frequency (Hz)	1178(152)	1664(133)	<0·001	1178(119)	1221(127)	n.s
Ulnar peak flow frequency (Hz)	858(140)	1433(161)	<0·001	1041(210)	1075(169)	n.s

Values are mean(s.e.m.); n s , not significant

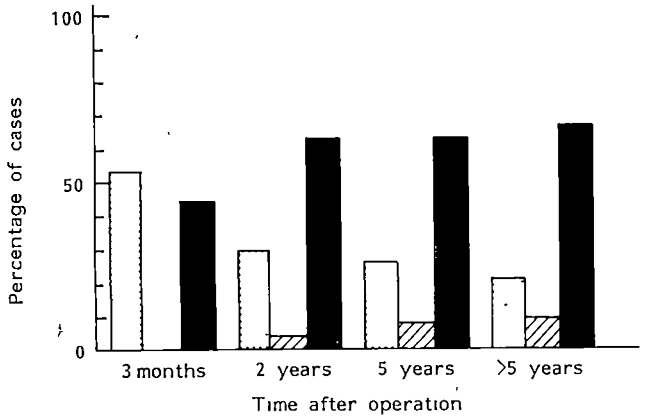

Figure 2 *Results in 15 patients (22 operations) after resympathectomy in relation to the time to recurrence of symptoms after operation* ■, *Poor results,* ▨, *fair results,* ☐, *good results*

Secondary Raynaud's phenomenon

In this phenomenon the clinical symptoms are similar to those in primary Raynaud's disease, although based on a proven underlying disorder

Three reoperations were performed in three patients (all women) aged 49, 50 and 61 years. Progressive systemic sclerosis was the underlying disease, verified by skin biopsies or oesophageal radiographic examination.

Asphyxia manus et digitorum

This condition is characterized by a sharply bordered white and sometimes cyanotic discoloration of one or more fingers or of the hand. The underlying disease is an obstructed digital artery lesion This local ischaemic phenomenon is hereafter termed 'asphyxia'

Seven patients (two women, five men) were classified as having asphyxia The mean age in this group was 50 years (range 32–60 years) and eight sides were operated on One man had thromboangiitis as the underlying disease and he had a bilateral operation. Two patients had atherosclerosis and one patient had a hypothenar hammer syndrome Microemboli were found in three patients but their origin could not be found in two. In one case a thoracic outlet syndrome was considered as the source. In this patient the first rib was resected at reoperation.

Post-traumatic dystrophy

Two reoperations were performed in two women aged 36 and 40 years. The indication for operation was continuous burning pain. Diagnosis was made by clinical history, physical and radiographic examination.

The criteria for the classification of the effect of sympathectomy corresponded with criteria used by other authors[15–19]. The long-term results are presented in relation to the time of symptom recurrence after operation. All patients, except one who died in the follow-up period, were seen for re-examination by the authors The mean follow-up period was 6·9 years (range 3–12 years).

In 14 patients continuous wave Doppler ultrasonography data from radial and ulnar arteries were available from before and after operation. These yielded objective data[20] of a successful operation As a result of vasodilatation following sympathectomy, a decrease in peripheral resistance can be expected Differences in peak forward frequency are accepted as being characteristic of changes in peripheral resistance[21] Signals from the non-operated side were used as a frame of reference To evaluate the statistical significance between two measurements Student's *t* test was used.

Results

Direct subjective improvement after resympathectomy was seen in 21 patients (27 operations). In 14 of these patients continuous wave Doppler data were available. A statistically significant increase in peak forward frequency was found after surgery on the operated side ($P<0{\cdot}001$) (*Table 1*).

In six patients (eight operations) no relief of symptoms was achieved after reoperation. Five of these patients (seven operations) were diagnosed as having primary Raynaud's phenomenon and one as suffering from secondary Raynaud's phenomenon with progressive systemic sclerosis as the underlying disease. The analysis of the results is presented separately for each group.

Primary Raynaud's phenomenon (Figure 2)

Within 3 months a high percentage of poor results (45 per cent) was found, not only because of recurrence of symptoms but especially because five patients (seven procedures) had no improvement at all after resympathectomy. After 2 years 70 per cent of patients had recurrence of their symptoms In the long term 32 per cent of patients, when fair results are included, were improved by reoperation.

Secondary Raynaud's phenomenon

Of the three patients with secondary Raynaud's phenomenon, no improvement was seen in one and another had relief of symptoms only for a period of several months. The third patient died from cardiac arrest before a final re-evaluation She had already been treated several times with plasmapheresis because of a return of symptoms.

Asphyxia

Good results were achieved from all eight procedures in the period immediately after operation. In three cases, however, relapse occurred to the same stage of severity as before operation. The other five patients were free from symptoms at the time of re-examination. The follow-up period was more than 6 years in these cases.

Post-traumatic dystrophy

Two patients were treated for post-traumatic dystrophy. One patient was relieved of all pain. The other patient had symptoms, although she claimed to be improved compared with her preoperative state.

Complications

No serious complications were seen after operation except for two patients (7 per cent) who developed Horner's syndrome and two patients with pneumothorax. Complaints of long-lasting pain around the scar and in the back were noted in 60 per cent of patients.

Discussion

Many possible explanations for the frequent relapses after sympathectomy are already known. An anatomical study of resection specimens after the thoracodorsal sympathectomy *en bloc*[22] forms the basis for the following explanations.

Alternative pathways in the upper paravertebral region may explain the early relapses. It is possible that these pathways remain intact after operation and subsequently replace the function of the resected sympathetic fibres. Relapses in the long term may be explained by regeneration of divided fibres. Analysis of patients who underwent thoracic resympathectomy lends support to both these explanations In 77 per cent of cases a successful resympathectomy with the *en bloc* operative technique was seen and these patients clearly showed subjective improvements of their symptoms, most probably because of resection of sympathetic fibres. Patients with early relapses or no relief at all after the previous sympathectomy, as well as patients with relapses in the long term, are included. Confirmation of these subjective results is available from the objective continuous wave Doppler data in 14 patients.

Only a few authors have reported their experience after reoperation in the literature. In 1951 Jepson[23] described a patient who was re-explored by the posterior route 2 years after the original operation A neuroma at the end of the sectioned sympathetic chain was found but there were no anatomical connections in between. No evidence of regeneration as a cause of relapse was found. He was not able to cure the patient. Cohen[24] in 1953 confirmed the absence of regeneration at re-exploration The experience of Peacock[25] in reoperations was that removal of the scar tissue on the side of the previous operation, together with excision of the stellate ganglion, was followed by vasodilatation of the vessels of the upper extremity. However, after this reoperation his patients had no long-term benefit. Haxton[7,26] also believed that resympathectomy of the upper extremity was possible. He reoperated on one patient by clearing away the fibrous tissue over the heads of the second and third ribs on each side. No Horner's syndrome resulted, but the hands became hot and dry and sympathetic activity was ablated, contrary to the situation before surgery. The preoperative presence of sympathetic fibres was confirmed by ulnar nerve blockade. The only likely explanation for the relapse was regrowth of divided fibres, so restoring functional continuity. Mattassi *et al.*[27] made a special plea to reserve the axillary approach for reoperation. In one case they found a normal sympathetic chain without interruption, although in the first operation histological confirmation of removal of the second and third ganglia had been obtained Their explanation was complete regeneration of the sympathetic chain.

The results presented in this study show that a sympathectomy effect is possible after reoperation. The long-term results showed the same pattern in all groups of patients as that found in the literature after primary sympathectomy[2,17,27,28]. In patients with primary or secondary Raynaud's phenomenon the results were disappointing. It was obvious that in five patients (seven operations) with primary Raynaud's phenomenon no relief of symptoms could be achieved. The same disappointing results occurred after the original operation in these three patients. A possible explanation might be found in anatomical variation. The extensive resection technique used for reoperation may still not be extensive enough to interrupt all the sympathetic fibres to the affected extremity. The best results were obtained in patients with asphyxia, although in one patient with thromboangiitis, who did not stop smoking, the progress of the disease was severe. After 6 months of relief, necrotic skin lesions occurred and amputation of three fingers was necessary.

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Endoscopic transthoracic electrocautery of the sympathetic chain for palmar and axillary hyperhidrosis

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Endoscopic transthoracic electrocautery of the sympathetic chain has been the preferred treatment for palmar or axillary hyperhidrosis in this unit since 1980. A retrospective study was carried out of the first 112 patients with case material derived from a postal questionnaire, chart review and outpatient assessment. Eighty-five patients undergoing bilateral transthoracic electrocautery who replied to the questionnaire (76 per cent response rate) form the basis of this study. There were 65 females and 20 males with a mean age of 24·3 years (range 15–40 years). The hands alone were affected in 20 patients (24 per cent), the axillae alone in 17 (20 per cent) and both areas in 48 (56 per cent). Mean hospital stay was 3·1 days (range 1–7 days). Outcome was assessed by 92 per cent of patients immediately after operation as 'very much improved' or 'moderately improved', and this assessment persisted in 85 per cent after a mean follow-up of 43 months (range 3–95 months). Cosmetic results were rated as satisfactory by 95 per cent. Apart from pain after operation, morbidity was limited to transient Horner's syndrome in three patients, surgical emphysema in three, and pneumothorax requiring a chest drain in one. A repeat procedure was needed in one patient because of an inadequate first operation. Some compensatory hyperhidrosis occurred in 54 (64 per cent) patients. As a minimally invasive procedure, endoscopic transthoracic electrocautery should be considered the treatment of choice for palmar and axillary hyperhidrosis.

Keywords: Hyperhidrosis, sympathectomy, minimally invasive surgery

Hyperhidrosis is a pathological condition in which sweating occurs in excess of that required for thermoregulation. It can be very distressing and a source of intense embarrassment, interfering with social and work commitments. It may be primary, with no obvious underlying cause, or secondary to a variety of neurological or systemic diseases such as thyrotoxicosis and phaeochromocytoma. Epidemiological data are scant, but Adar *et al.* suggest an incidence of 0·6–1·0 per cent[1]. Symptoms usually appear at puberty but may date back to early childhood and usually persist throughout adult life. Hyperhidrosis is usually localized to the palms, axillae and feet, but the face, back, groin and legs may also be affected.

The management of hyperhidrosis remains controversial[2]. Medical treatment is effective only in the mildest cases. Biofeedback techniques have been used with limited success[3]. Treatment with iontophoresis is messy and time consuming with short-lived effect[4,5]. Local excision of sweat glands has a role only where the disease is confined to the axilla[6,7]. Sympathectomy remains the cornerstone of surgical management. Various operative approaches have been described, each with its advocates: the cervical or supraclavicular approach[8], the posterior approach[9], the transaxillary approach[10] and transthoracic endoscopic sympathectomy[11]. The reported incidences of side-effects following sympathectomy have varied considerably, especially that of compensatory hyperhidrosis (excessive sweating in other areas following a successful procedure)[12–14]. Patient satisfaction with the cosmetic result is also variable[15].

The aims of this study were to examine the pattern of presentation of hyperhidrosis and the result of treatment with endoscopic transthoracic electrocautery, with particular reference to the complications of surgery, the immediate and long-term effectiveness of treatment, and patient satisfaction with the cosmetic result.

Patients and methods

All patients had been referred with incapacitating hyperhidrosis which interfered with their work or with social activities Patients who appeared to have a psychological component to their sweating were not operated on. Those with excessive axillary sweating were first treated with 20 per cent aluminium chloride (Anhydrol Forte®, Dermal Laboratories Ltd., Gosmore, UK) and were operated on only if this was ineffective. Routine laboratory and radiological screening tests, including full blood count, sedimentation rate, urea and electrolyte estimation, thyroid function studies and chest radiography, were carried out on all patients to preclude an underlying cause All were carefully counselled on potential complications of the operation such as postoperative pain, pneumothorax and compensatory hyperhidrosis Patients with a clinical history suggesting pleural adhesions or radiological evidence of pleural thickening were not offered the procedure. It is estimated that of all patients referred to this unit because of the expressed interest in this minimally invasive technique, one-third were reassured and discharged following investigation, one-third were managed medically, and approximately one-third underwent transthoracic endoscopic cautery.

Surgical technique

The procedure was performed under general anaesthesia using a double lumen endotracheal tube. The patient was placed in the supine position with both arms abducted to 90° Blood pressure and heart rate were monitored throughout

An artificial pneumothorax was established by insufflating 0·5 litres of carbon dioxide through a Veress needle (Storz Medical Instrument Company, Tutlingen, FRG) in the fourth intercostal space, having first

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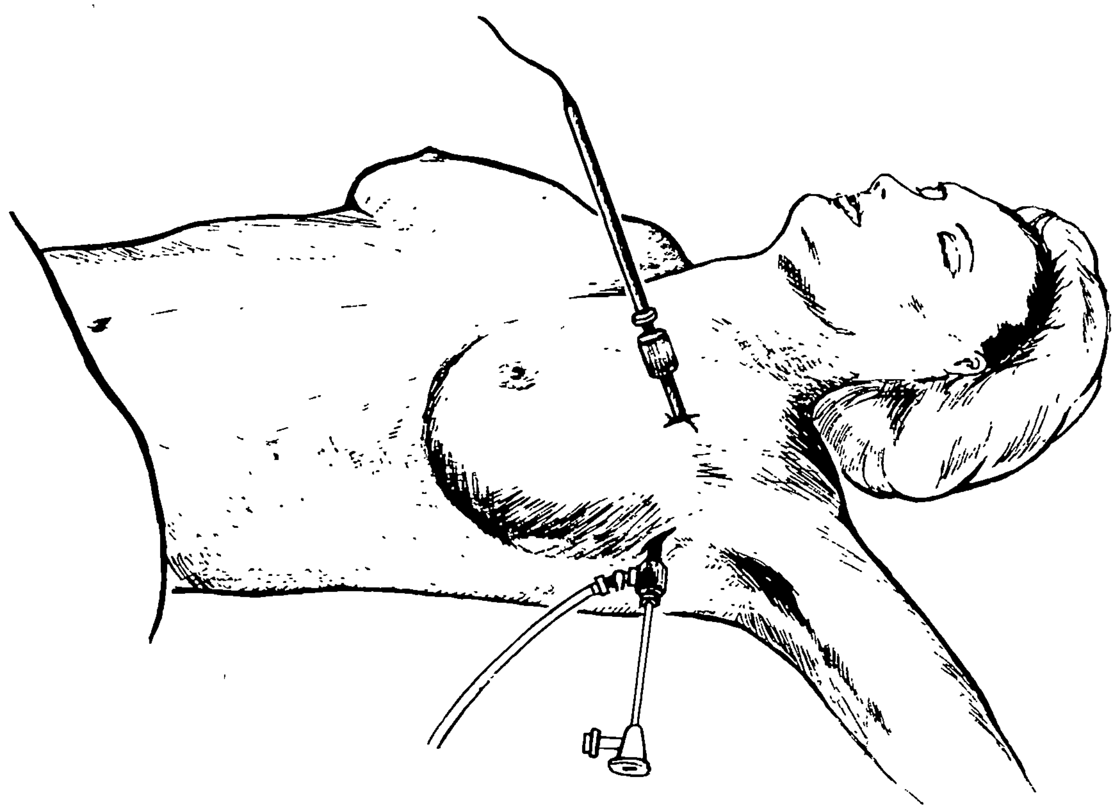

Figure 1 *Position of patient and sites of insertion of laparoscope and diathermy probe*

disconnected the ipsilateral portion of the endotracheal tube from the ventilator. A small incision was made in the fourth intercostal space in the anterior axillary line and a Storz laparoscope was introduced through a cannula (*Figure 1*). More carbon dioxide was introduced and the upper lobe of the lung was observed as it collapsed. Flimsy adhesions were cut with diathermy scissors but major apical adhesions could render the operation impossible.

The sympathetic chain was usually visualized under the parietal pleura running down over the necks of the second, third, fourth and fifth ribs (*Figure 2*). A unipolar diathermy probe was inserted through a separate stab incision, usually in the midclavicular line. If the chain was not easily seen due to subpleural fat it could be located by stroking the diathermy probe along the neck of the rib The chain was then felt and seen as it slipped out from under the tip of the probe. The pleura over the chain was incised with diathermy and the second, third and fourth thoracic ganglia and intervening chain were electrocoagulated until they presented a charred appearance The fifth ganglion was included for denervation of the axilla The stellate ganglion could not be seen as it is covered by a characteristic yellow fat pad

On completion of the first side, the endobronchial tube was reconnected and the lung was reinflated allowing the carbon dioxide to escape through the cannula. The progress of reinflation was checked visually through the laparoscope. The procedure could be repeated on the opposite side under the same anaesthetic. This has caused no problems in our experience. It is important, however, to monitor pulse rate and blood pressure carefully throughout the entire procedure to guard against inadvertent pneumothorax, and the carbon dioxide line pressure should not exceed 10 cmH$_2$O

A chest radiograph was performed after operation in the recovery room. Chest drains were not used except in two early cases where oozing could not be fully controlled by direct pressure.

Postal questionnaire

A detailed postal questionnaire was sent to all patients and information was requested about. (i) the areas affected by hyperhidrosis before operation, (ii) the presence of a family history of hyperhidrosis; (iii) the effectiveness of transthoracic endoscopic cautery immediately following surgery; (iv) its effectiveness at the time of follow-up, with results graded as 'very much improved', 'moderately improved', 'slightly improved', 'same' and 'worse' than before operation; (v) the cosmetic result which was graded as 'excellent', 'good', 'fair' or 'poor'; (vi) the occurrence of postsympathectomy pain, (vii) the incidence and severity of compensatory hyperhidrosis; (viii) the sites of, and precipitating factors for, compensatory sweating; (ix) whether compensatory hyperhidrosis persisted or faded with time; and (x) the time it took to disappear.

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Hospital in-patient files were retrieved and analysed to obtain the extent of the sympathectomy, the duration of in-patient stay and the incidence and severity of postoperative problems.

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One hundred and twelve patients were circularized. Eighty-five (76 per cent) returned a completed questionnaire and were included in the study. All of these patients had undergone bilateral transthoracic electrocautery. There were 65 females and 20 males of mean age 24·3 years (range 15–40 years). The areas affected before operation were hands alone in 20 (24 per cent) patients, axillae alone in 17 (20 per cent) patients and both areas in 48 (56 per cent) patients. In addition, 16 patients complained of excessive sweating affecting the trunk, 17 of excessive sweating affecting the groin and 45 of excessive sweating of the feet. In all cases, however, it was hyperhidrosis of hands and axillae which had caused them to seek surgical attention. Thirteen patients (15 per cent) reported an affected parent (five mothers, eight fathers) while 29 (34 per cent) reported one or more affected siblings One patient had an affected mother and sibling while five had both father and sibling affected.

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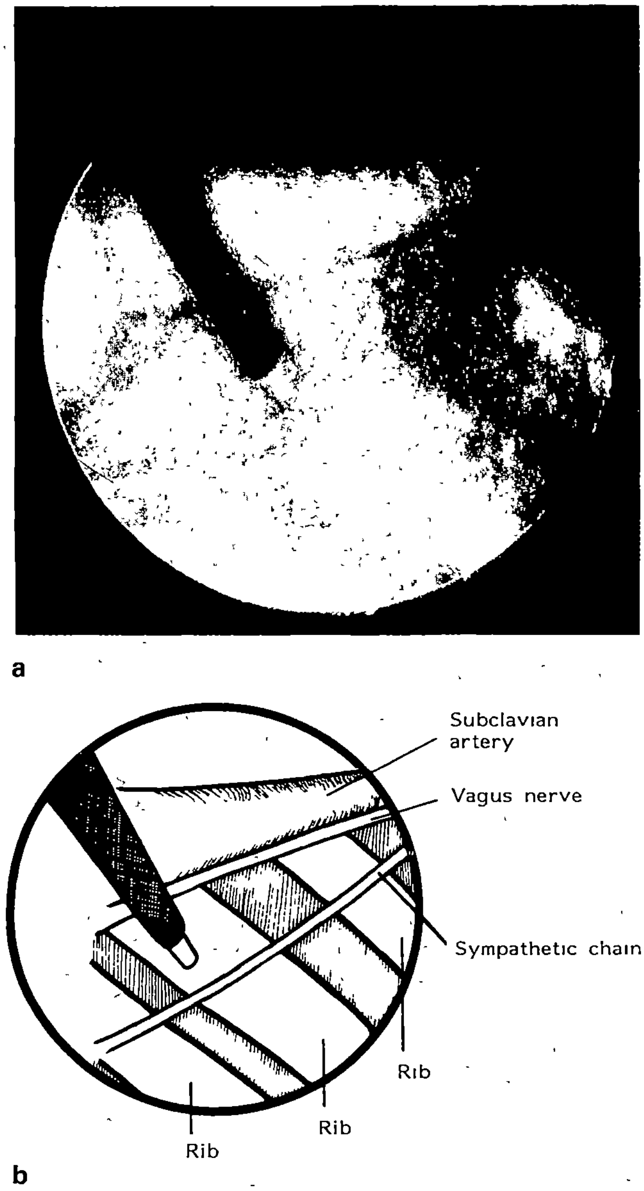
In all but one patient the hands and/or axillae were recorded as dry on returning from the operating theatre. In one early case the procedure was unsuccessful and had to be repeated Seventy-eight of the 85 patients reported immediate satisfaction with the procedure (*Table 1*).

There was no mortality and no serious morbidity in this series. Horner's syndrome occurred in three patients, resolving in two by 6 weeks and in one by 6 months. Surgical emphysema



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Assessment	Immediately after operation	At follow-up
Very much improved	67 (79)	65 (76)
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was noted in three patients and a pneumothorax requiring a chest drain occurred in one patient. One patient suffered a wound infection. Other transient postoperative phenomena included chest pains (eight patients), paraesthesia or numbness in the arms (five patients), back pain (four patients), and Raynaud's phenomenon (four patients). The mean duration of hospital stay was 3·1 days (range 1–7 days).

Late results

The mean follow-up period was 43 months (range 3–95 months). Patients' assessment of the effectiveness of surgery in treating their hyperhidrosis is given in *Table 1*. Follow-up was greater than 3 years in 47 patients, seven of whom reported some deterioration in outcome compared with that immediately after operation. In four of the seven, symptoms were still better than at the time of initial presentation. A further four patients recorded improvement over the same period.

The cosmetic result was graded as good by 68 (80 per cent) patients, moderate by 13 (15 per cent) and fair by four (5 per cent). No patient expressed dissatisfaction with the result in terms of cosmesis.

Some compensatory hyperhidrosis occurred in 54 (64 per cent) patients. This persisted in 44 patients, fading in only ten, with a mean fade-out interval of 10·1 months (range 1–30 months). It was described as less distressing than the original sweating in the majority but did warrant further investigation and treatment in four patients; this accounted for the reported 'worsening' of their overall condition. The sites affected by compensatory hyperhidrosis are given in *Table 2* and precipitating causes are given in *Table 3*.

Discussion

Endoscopic transthoracic electrocautery is a minimally invasive procedure with several advantages over open surgery in the treatment of palmar and axillary hyperhidrosis. It is quick and easy to perform. It provides excellent visualization of the sympathetic chain, better in fact than open surgery, and the stellate ganglion lying beneath a fat pad is relatively protected. Postoperative pain, a feature particularly of the axillary approach, is minimized, and a difficult dissection, as in the cervical approach, is avoided. The duration of hospital stay is reduced to a minimum.

The technique described here differs from the original description of Kux[16] in a number of details. A double lumen endotracheal tube was used and both sides were dealt with at the same operation. Chest drains were not routinely used and this has not caused any increased patient morbidity. We favour passing the diathermy probe through a separate stab incision, permitting the use of a finer laparoscope which is useful in younger patients with narrow intercostal spaces, and which may reduce postoperative chest pain.

Postoperative complications were few and the incidence of permanent Horner's syndrome and of significant pneumothorax compares favourably with the results of Greenhalgh *et al.*[17] who reported Horner's syndrome in 14 per cent and pneumothorax in 16 per cent of patients, and with those of

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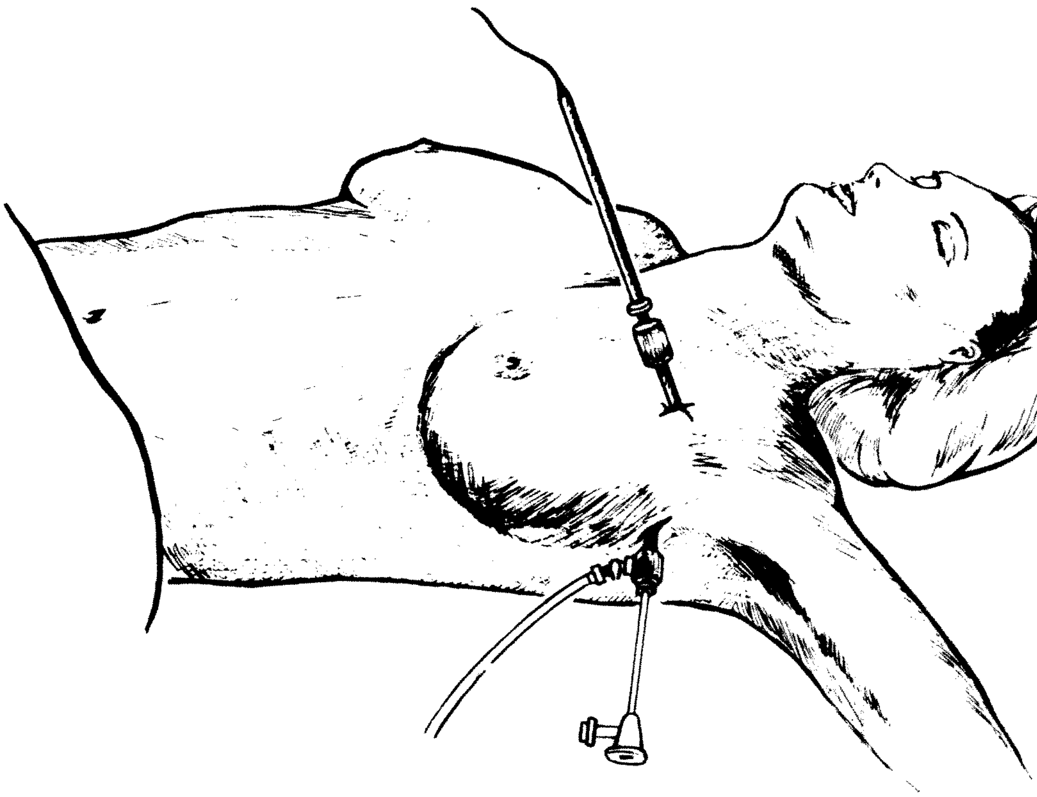

Figure 1 *Position of patient and sites of insertion of laparoscope and diathermy probe*

disconnected the ipsilateral portion of the endotracheal tube from the ventilator. A small incision was made in the fourth intercostal space in the anterior axillary line and a Storz laparoscope was introduced through a cannula (*Figure 1*). More carbon dioxide was introduced and the upper lobe of the lung was observed as it collapsed. Flimsy adhesions were cut with diathermy scissors but major apical adhesions could render the operation impossible.

The sympathetic chain was usually visualized under the parietal pleura running down over the necks of the second, third, fourth and fifth ribs (*Figure 2*). A unipolar diathermy probe was inserted through a separate stab incision, usually in the midclavicular line. If the chain was not easily seen due to subpleural fat it could be located by stroking the diathermy probe along the neck of the rib. The chain was then felt and seen as it slipped out from under the tip of the probe. The pleura over the chain was incised with diathermy and the second, third and fourth thoracic ganglia and intervening chain were electrocoagulated until they presented a charred appearance. The fifth ganglion was included for denervation of the axilla. The stellate ganglion could not be seen as it is covered by a characteristic yellow fat pad.

On completion of the first side, the endobronchial tube was reconnected and the lung was reinflated allowing the carbon dioxide to escape through the cannula. The progress of reinflation was checked visually through the laparoscope. The procedure could be repeated on the opposite side under the same anaesthetic. This has caused no problems in our experience. It is important, however, to monitor pulse rate and blood pressure carefully throughout the entire procedure to guard against inadvertent pneumothorax, and the carbon dioxide line pressure should not exceed 10 cmH_2O.

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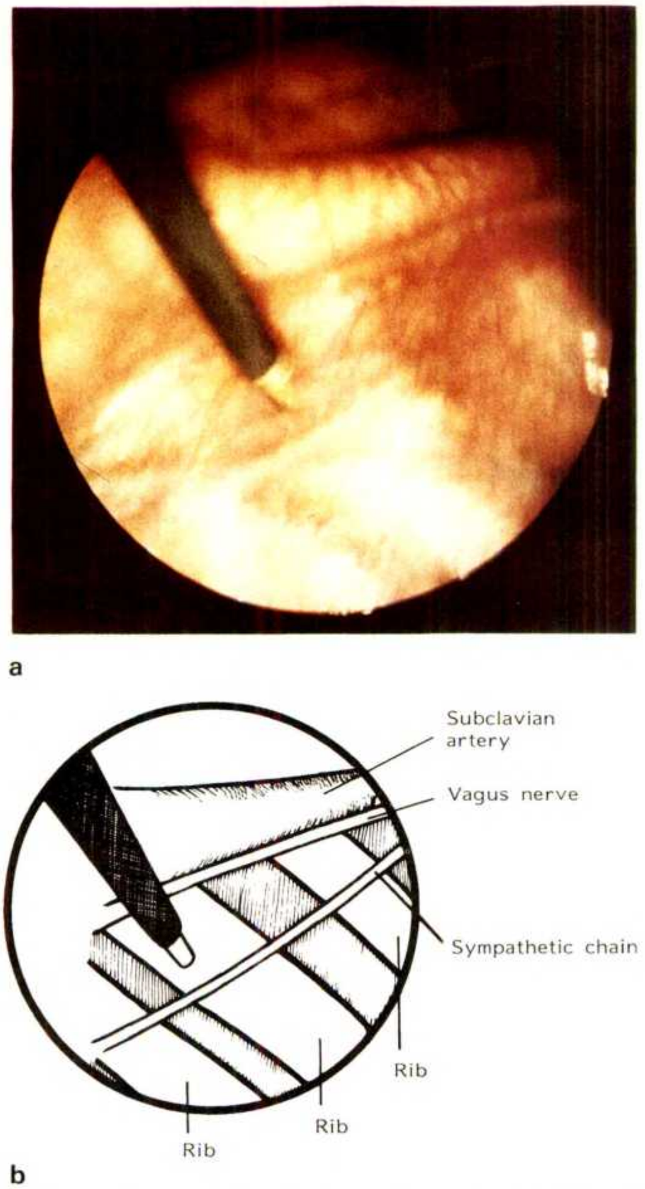

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Adar *et al.*[1] who reported Horner's syndrome in 57 per cent and pneumothorax in 6 per cent. Complications of the open approaches such as brachial plexus contusion and recurrent laryngeal nerve paralysis are obviated.

Ninety-two per cent of patients who initially showed improvement following transthoracic cautery maintained this improvement at follow-up suggesting that lasting relief is obtained. These results are unlike those following sympathectomy for Raynaud's disease. Patient satisfaction with cosmesis is especially gratifying as this is an elective procedure in a young, predominantly female, population. The cosmetic result contrasts markedly with that after open surgery using the transaxillary approach after which up to 29 per cent of patients have reported dissatisfaction[15].

Compensatory hyperhidrosis, which has long been recognized as a complication of sympathectomy[18], occurred in 64 per cent of patients, which is similar to the incidence reported by other authors[1,13,14,16]. The cause of compensatory sweating following sympathectomy remains obscure. Guttmann[19] was amongst the first to describe 'perilesionary' hyperhidrosis and considered it a compensatory response associated with heat regulation, whereas Monro[20] attributed it to a special supraspinal reflex. Shelley and Florence[21] suggested that postsympathectomy hyperhidrosis is compensatory and serves a thermoregulatory function. Using Berkov's surface-area formulae they calculated that up to 40 per cent of sweat gland function is lost following bilateral cervical sympathectomy and suggested that all patients who have had extensive sympathectomy will show compensatory hyperhidrosis to heat stress. They stated that neither foods nor emotions ever triggered the response. This is at variance with the present findings where gustatory sweating was a frequent and occasionally troublesome feature and stress was identified clearly as a precipitating factor. Shelley and Florence noted that the trunk was most frequently affected, and this was also the case in the present study. Compensatory hyperhidrosis, however, was only a minor inconvenience to most patients compared with the original problem. In a minority (5 per cent), it was severe enough to warrant further investigation and responded, at least partially, to medical therapy.

In summary, endoscopic transthoracic electrocautery is a safe, simple and cosmetically acceptable procedure for hyperhidrosis, which gives an effective, long-lasting result in the majority of patients. However, patients should be advised of the possibility of compensatory hyperhidrosis.

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Transcutaneous oxygen tensions in assessing the treatment of healed venous ulcers

Transcutaneous oxygen tension (P_{tc,O_2}) was assessed as an indicator of risk of reulceration in 68 limbs with healed venous ulcers. P_{tc,O_2} was also used to assess two methods of ulcer prophylaxis. Measurements were made over the gaiter skin, the healed ulcer and the upper arm. The results were expressed as a ratio of the lower limb readings over those taken from the arm. Patients were randomized, after the ulcer had healed, to elastic stockings and stanozolol, or elastic stockings and surgical ligation of incompetent superficial veins. Patients who declined to participate in the study were prescribed elastic stockings only. Those limbs remaining healed at 12 months had P_{tc,O_2} ratios remeasured. The P_{tc,O_2} ratios from limbs that reulcerated were not significantly lower than those from limbs remaining healed. The P_{tc,O_2} ratio was significantly increased in limbs treated by stanozolol and elastic stockings ($P < 0.05$) and by surgery and elastic stockings ($P < 0.05$). There was no significant increase in P_{tc,O_2} in limbs treated by elastic stockings alone. In those treated by surgery and elastic stockings, there was a significant improvement in limbs with normal deep veins ($P < 0.01$), but not in limbs with post-thrombotic changes on ascending phlebography. Although these two methods of ulcer prophylaxis improve the P_{tc,O_2} ratio, a high ratio has not been shown to be beneficial in preventing ulcer recurrence.

Keywords: Venous ulcer, elastic stockings, ascending phlebography, skin hypoxia, venous surgery

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Induration, pigmentation and inflammation of the gaiter skin above the ankle, which is called lipodermatosclerosis, is known to precede venous ulceration[1]. These changes are associated with fibrin deposits in the dermis of the affected skin[2]. The fibrin may act as a diffusion barrier to oxygen transport, resulting in hypoxia of the overlying skin, which in turn may lead to tissue necrosis and ulceration[3]. This theory of skin hypoxia has been supported by the demonstration of reduced fractional oxygen extraction from the blood in limbs with lipodermatosclerosis and venous ulceration, using the positron emission scanner[4]. Other studies have also shown a reduced transcutaneous oxygen tension (P_{tc,O_2}) over lipodermatosclerotic skin compared with normal skin[5,6].

Initial efforts to improve areas of lipodermatosclerosis and reduce the incidence of reulceration after healing were directed at improving the efficiency of the calf muscle pump, using graduated compression elastic stockings[7], ligation of incompetent lower leg communicating veins combined with eradication of other surface varicosities[8] and, more recently, deep venous reconstruction and valve transplantation or repair[9]. Attempts have also been made to treat lipodermatosclerosis by enhancing systemic fibrinolytic activity[10].

In this study, transcutaneous oxygen tensions have been measured after ulcer healing to discover whether this measurement gives any indication of which ulcers will subsequently break down. Patients whose venous ulcers had healed were randomized to surgical eradication of incompetent surface varicosities and ligation of the calf communicating veins, or to oral administration of stanozolol to enhance fibrinolysis. Both groups were prescribed graduated compression elastic stockings. Transcutaneous oxygen measurements were made after the ulcer had healed and 1 year after treatment to discover if either form of treatment had produced a measurable improvement.

Patients and methods

Patients were entered into the study when their venous ulcers had healed. Patients with other types of leg ulcer were excluded by investigation. Estimations of haemoglobin, erythrocyte sedimentation rate, urea and electrolytes, liver enzymes and bilirubin, blood glucose, Rosewaaler titre, rheumatoid factor latex fixation, antinuclear antibody titre and arterial Doppler ankle:brachial pressure index were made for all patients. All limbs had ascending phlebography using the technique described by Lea Thomas[11], and foot volume plethysmography using a modification[12] of the method described by Norgren[13]. The previously ulcerated limbs all had evidence of abnormal venous reflux as measured by foot volume plethysmography (an abnormal half volume refilling time), and many showed evidence of post-thrombotic damage or incompetence of the ankle communicating veins on ascending phlebography. None of the limbs that were included in this study had any other obvious cause of ulceration.

Patients were randomized into two treatment groups. One group had ligation of the incompetent lower leg communicating veins combined with eradication of all other visible incompetent varicose superficial veins (i.e. the long and short saphenous veins and their tributaries), and the other group was given stanozolol 5 mg twice daily for 9 months. Both groups were supplied with below-knee graduated compression elastic stockings (Sigvaris, Ganzoni and Cie AG, St. Gallan, Switzerland) which were worn continuously and replaced every 6 months. Patients who declined to participate in the study were prescribed graduated compression elastic stockings and were encouraged to wear them every day.

Skin hypoxia was estimated using a transcutaneous oxygen monitor (TCM2, Radiometer, Copenhagen, Denmark). The electrode was heated to 45°C. With the patient lying supine, measurements were taken at a point 7·5 cm above the medial malleolus on both legs, over the site of the recently healed venous ulcer, and on the anterior aspect of the upper arm, which was used as a control site. The results of the transcutaneous oxygen measurements were expressed as a ratio of the reading from the gaiter skin divided by the reading from the upper arm. Like others, we have found less variation in the leg-to-arm ratio than in absolute readings on repeat testing[14].

Transcutaneous oxygen tensions were measured when the venous ulcers had healed. Patients were seen on a regular basis in the outpatient clinic to determine the incidence of reulceration. Those patients with limbs that did not reulcerate had transcutaneous oxygen tension measurement repeated 12 months after the start of treatment. Patients with recurrent ulceration did not have repeat measurement at 12 months because the recurrent ulcer was invariably at the site of the previously healed ulcer, and in almost half of these patients this either involved or was immediately adjacent to the standard site of measurement, making a proper repeat measurement impossible.

Statistical analysis was performed using the Wilcoxon paired rank sum test for paired data, and the Wilcoxon rank sum test for unpaired data.

Results

Sixty-eight limbs had transcutaneous oxygen ratios measured when their venous ulcers had healed and were then treated by one of the three methods described. The 55 patients involved were followed regularly in the outpatient clinic. There were 29 men and 26 women of age 30–80 years with a median of 60 years. Twenty-five limbs (20 patients) were treated by surgery and elastic stockings, 24 limbs (17 patients) were treated by stanozolol and elastic stockings, and 19 limbs (18 patients) were treated by elastic stockings alone.

A further 17 patients who had initially been entered into this study were later withdrawn owing to failure to undertake the treatment; eight patients were in the stanozolol and stockings group (three did not take the tablets, four did not attend for follow-up, and one died soon after entering the study) and nine were in the surgery and elastic stockings group (two refused operation, one was not fit for operation, three did not attend when called in for operation, one had his operation but did not attend for follow-up, and two were still awaiting operation after 12 months). There was no side-effect from stanozolol in any of the 17 patients.

Repeat measurements 12 months after treatment were made in 56 limbs; 24 (19 patients) treated by surgery and elastic stockings, 18 (12 patients) by stanozolol and elastic stockings, and 14 (13 patients) by elastic stockings only. Repeat measurements were not made in the other 12 limbs because they reulcerated during the study period and the treatment was then changed. Recurrent ulceration occurred in a further four limbs after the repeat readings had been performed; two were treated by surgery and elastic stockings, and two were treated by stanozolol and elastic stockings.

There was no significant difference in age or sex distribution between any of these groups. All limbs studied had an abnormal half volume refilling time on foot volume plethysmography. The distribution of post-thrombotic changes as determined by ascending phlebography were similar for the three groups (*Table 1*).

The effect of the conditions under which readings were performed on both the absolute value from the leg and the ratio of the reading from the leg over the reading from the arm were assessed. In 15 limbs, transcutaneous oxygen measurement was made with the patient lying quietly at rest, and repeated after talking to the patient for 5 min. The reading from the leg and the reading from the arm increased significantly (initial median values for leg = 46 mmHg, arm = 69 mmHg; repeat values for leg = 56 mmHg, arm = 78 mmHg, $P<0{\cdot}01$ for each). However, there was no significant increase in the ratio (initial median value 0·70; repeat 0·71).

Table 1 *Distribution of post-thrombotic changes and normal deep veins on ascending phlebography in 68 limbs*

	Surgery and stockings	Stanozolol and stockings	Stockings alone
Limbs with normal deep veins	13	9 (4)	8 (1)
Limbs with post-thrombotic changes	12 (3)	15 (4)	11 (4)

Values in parentheses are numbers of limbs with reulceration

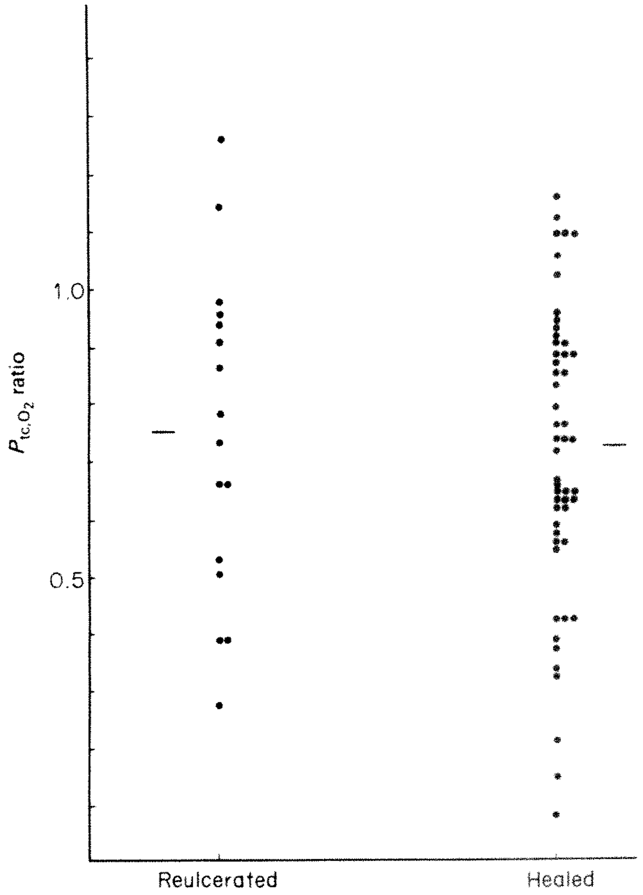

Figure 1 *Initial P_{tc,O_2} ratios from 7·5 cm above the medial malleolus in limbs which remained healed, and in those which reulcerated. No significant difference (Wilcoxon rank sum test, n = 68)*

The median P_{tc,O_2} ratio, taken from 7·5 cm above the medial malleolus after healing of the ulcer, was 0·73 (range 0·09–1·26), and from the site of the recently healed venous ulcer was 0·38 (range 0·03–1·40).

Patients have been followed to date from 6 to 37 months with a median of 16 months; 16 ulcers have recurred. The median time from the start of treatment to ulcer recurrence was 6 months (range 1–34 months).

There was no significant difference in the initial transcutaneous oxygen ratio, measured from the standard site on the leg, in those limbs that remained healed (median 0·72) compared with those that reulcerated (median 0·76) (*Figure 1*). The P_{tc,O_2} ratio from the site of the healed ulcer was significantly greater in limbs which reulcerated (median 0·51) than in limbs which remained healed (median 0·29, $P<0{\cdot}05$) (*Figure 2*). The number of repeat readings from the healed ulcer site was less than the number from the standard site on the leg because it was sometimes difficult to obtain a seal between the reading electrode and the irregular surface of a recently healed ulcer.

The repeat transcutaneous oxygen ratio from the site 7·5 cm above the medial malleolus for those limbs treated with surgery and elastic stockings improved significantly ($P<0{\cdot}05$) (*Figure 3*). There was also a significant improvement in those limbs treated by stanozolol and elastic stockings ($P<0{\cdot}05$) (*Figure 4*). There was, however, no significant improvement in those limbs treated by elastic stockings alone (*Figure 5*).

Limbs with and without post-thrombotic changes on ascending phlebography have been considered separately. In the surgery and elastic stocking treatment group, there was a significant improvement in the transcutaneous oxygen ratio in limbs without post-thrombotic changes ($P<0{\cdot}01$). There was

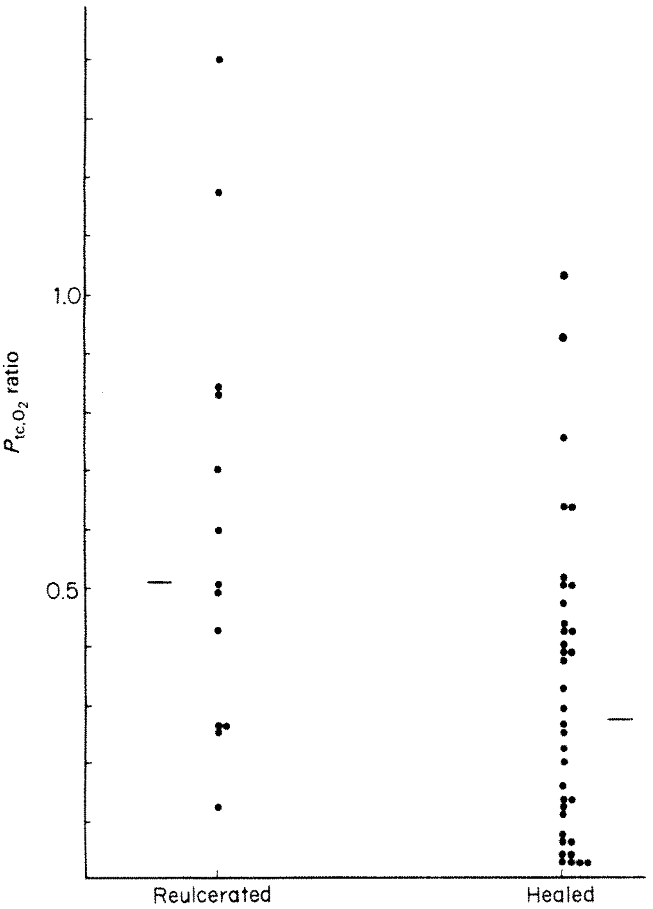

Figure 2 *Initial* P_{tc,O_2} *ratios from the site of the recently healed venous ulcer in limbs which remained healed and in limbs which reulcerated. Significantly lower ratios in the limbs remaining healed* ($P<0{\cdot}05$, *Wilcoxon rank sum test*) (n = *49*)

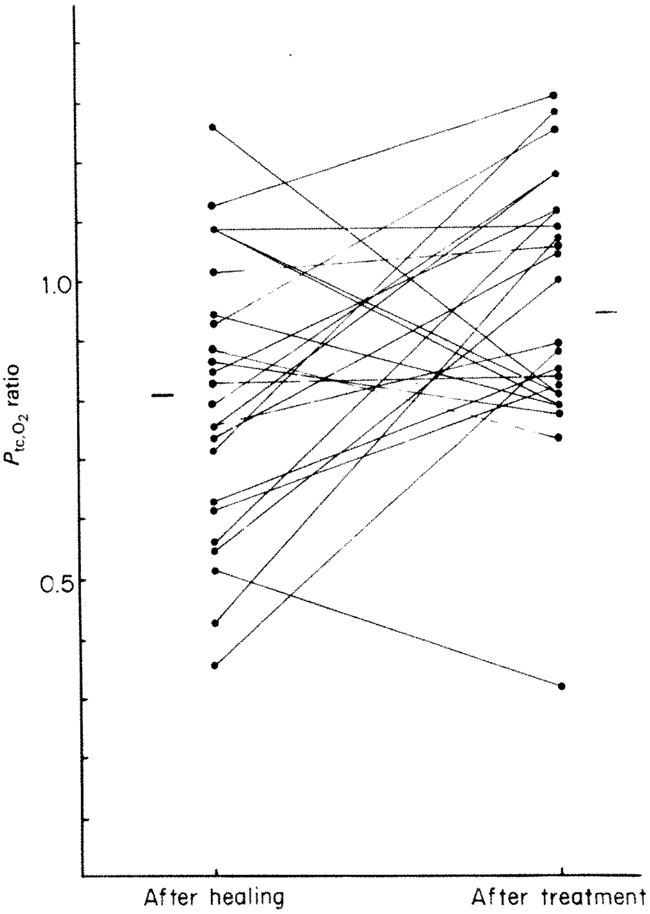

Figure 3 P_{tc,O_2} *ratios from 7·5 cm above the medial malleolus measured before and 12 months after starting treatment with surgery and elastic stockings* ($P<0{\cdot}05$, *Wilcoxon paired rank sum test*) (n = *24*)

no such improvement in the limbs with post-thrombotic changes (*Figure 6*). In the stanozolol and elastic stocking treatment group there was no significant improvement in the transcutaneous oxygen ratio in limbs with post-thrombotic changes or in limbs without such changes. Similarly, in the group treated by stockings alone, there was no improvement in the transcutaneous oxygen ratio in limbs with post-thrombotic changes or in limbs without such changes.

Discussion

This study confirms low transcutaneous oxygen tension over lipodermatosclerotic skin, with the lowest readings over the site of healed ulcer[5,6]. The reduced oxygen tension lends support to the theory that skin hypoxia may be an important factor in venous ulceration.

Unexpectedly, limbs which subsequently reulcerated did not have lower transcutaneous oxygen ratios after healing of a venous ulcer than limbs which remained healed. Indeed, ratios from recently healed ulcer sites were significantly higher in limbs that reulcerated than in limbs that remained healed. There is no ready explanation for this finding, which may be spurious because of the relatively low number of repeat measurements from limbs that reulcerated. However, one possibility is that skin over recently healed ulcers that break down may not be as thick as skin over healed ulcers that do not. This may allow more oxygen to diffuse through. Failure to demonstrate a clear separation in transcutaneous oxygen ratio between limbs that reulcerated and limbs that remained healed emphasizes the poor predictive value of the ratio for reulceration in the individual patient.

Factors other than skin hypoxia appear to play a significant role in causing recurrent ulceration. Local trauma, for example,

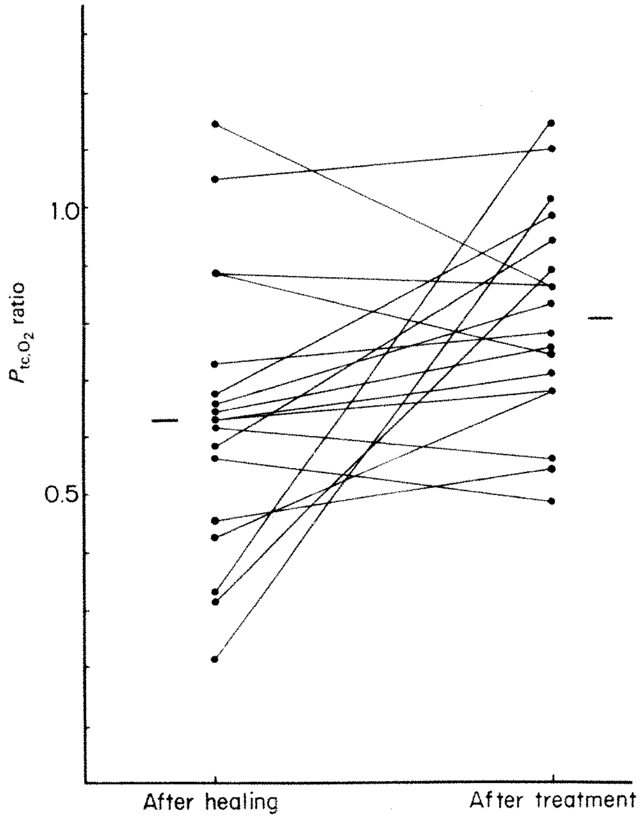

Figure 4 P_{tc,O_2} *ratios from 7·5 cm above the medial malleolus measured before and 12 months after starting treatment with stanozolol and elastic stockings* ($P<0{\cdot}05$, *Wilcoxon paired rank sum test*) (n = *18*)

may easily initiate reulceration, and it does not appear that improving local tissue oxygenation protects patients from the risk of skin breakdown.

A significantly improved transcutaneous oxygen ratio in limbs treated by stanozolol and elastic stockings and in limbs treated by surgery and elastic stockings has never been shown before. Improving either the calf muscle pump function by surgery, or the systemic fibrinolytic capacity by stanozolol, may reduce the barrier to diffusion of oxygen through the skin. This supports an earlier study which showed a greater reduction in the area of lipodermatosclerosis with stanozolol and elastic stockings than with elastic stockings alone[10].

Failure to demonstrate an improvement in transcutaneous oxygen ratio in limbs treated by elastic stockings alone may result from the relevant group not being randomized and being smaller than either of the other two groups. Treatment with elastic stockings alone still warrants further assessment before any definite conclusion may be made.

Improvement in transcutaneous oxygen ratio in limbs treated by surgery and elastic stockings appears to result solely from the improvement that occurred in those limbs with normal deep veins, as limbs with damaged deep veins did not change. This fits with previous findings that surgery to incompetent communicating veins does not prevent ulcer recurrence in post-thrombotic limbs[15], and that calf muscle pump function does not improve in post-thrombotic limbs after surgical ablation of superficial and incompetent lower leg communicating veins[16].

Treatment of limbs with definite radiographic evidence of post-thrombotic damage in the deep veins remains a difficult problem. In this study there was no improvement in the transcutaneous oxygen ratio in such limbs treated by surgery and elastic stockings. Although treatment with fibrinolytic enhancement and elastic stockings did seem to improve the ratio, this was a small group and statistical significance at the 5 per cent level was not achieved. The treatment of limbs with post-thrombotic changes on phlebography, by fibrinolytic enhancement and elastic stockings does warrant further assessment.

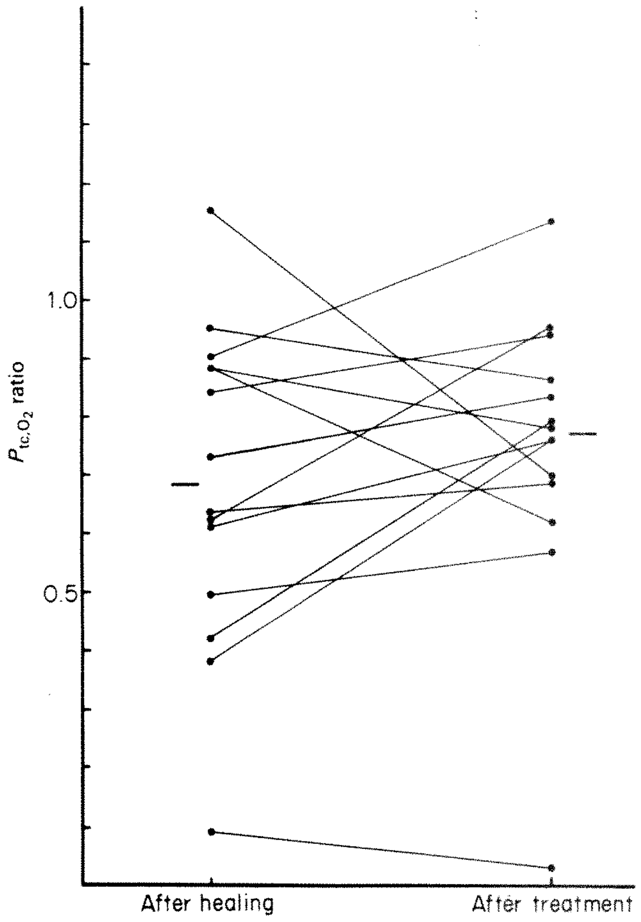

Figure 5 P_{tc,O_2} *ratios from 7·5 cm above the medial malleolus measured before and 12 months after starting treatment with elastic stockings alone. No significant difference (Wilcoxon paired rank sum test,* n = *14)*

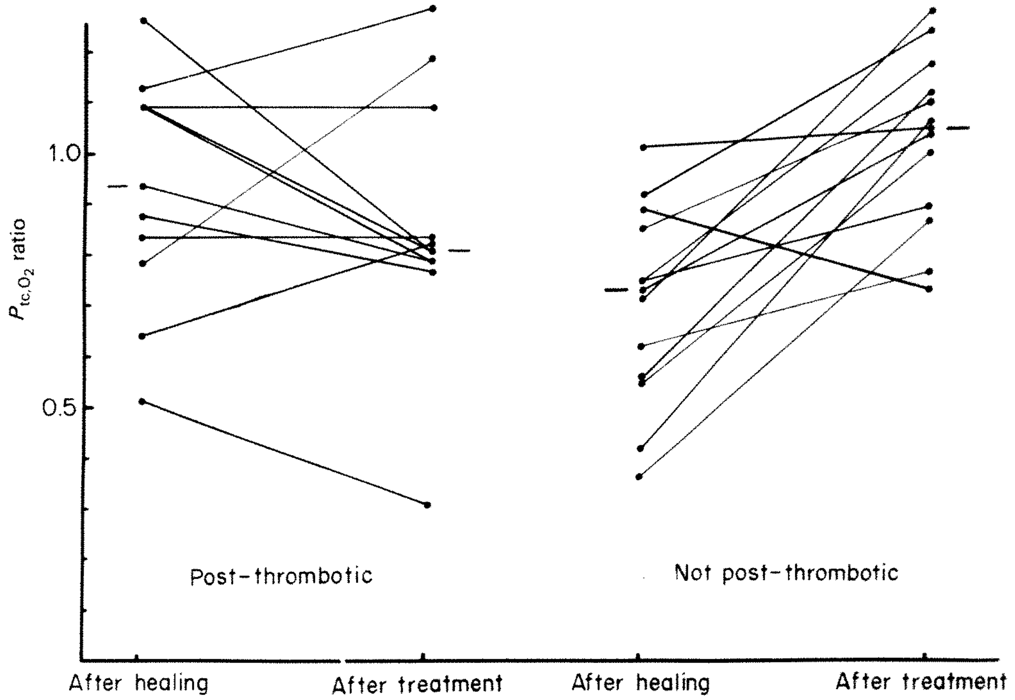

Figure 6 *Initial and repeat* P_{tc,O_2} *ratios in limbs with post-thrombotic changes* (n = *11, no significant difference, Wilcoxon paired rank sum test) treated with surgery and elastic stockings, and in limbs with normal deep veins* (n = *13, significant difference, Wilcoxon paired rank sum test,* $P<0{\cdot}01$*)*

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Venous stasis and vein lumen changes during surgery

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The mechanisms underlying the development of postoperative deep vein thrombosis remain to be fully elucidated. Previous studies have suggested that peroperative venous distension may be a factor associated with venous thromboembolism. In this study we have obtained high resolution ultrasound images of gastrocnemius and posterior tibial veins in 62 patients undergoing a range of general surgical procedures. From these we determined the changes in vein diameter occurring during the operative procedures, in response to induction of anaesthesia, and after completion of surgery. Veins showed no evidence of dilatation in response to the induction of anaesthesia, but by the end of the operative procedure showed distension of 22–28 per cent. Distension was most prominent in the gastrocnemius veins, and lesser distension was observed in the posterior tibial veins. In a series of patients who received an infusion of 1 litre of saline in addition to basal requirements, distension was 57 per cent compared with 22 per cent in the corresponding control group. Intraoperative venous distension is associated with factors that lead to deep vein thrombosis and may be involved in the mechanisms which result in the commencement of deep vein thrombosis.

Keywords: Deep vein thrombosis, pulmonary embolism, venous distension

Deep vein thrombosis and subsequent pulmonary embolism remain a significant hazard to hospital patients. In a recent study this pathological process was responsible for 10 per cent of deaths of patients who died in hospital[1]. Postoperative surgical patients accounted for 24 per cent of this series, emphasizing the continuing threat that deep vein thrombosis presents. The factors that may predispose patients to risk and the precautions that might prevent this problem are well known[2–4]. Although much research has been done into the pathogenesis of this problem, a complete understanding has yet to be achieved.

Virchow described the basic aetiology of venous thromboembolism more than a century ago[5]. Recent progress in many aspects of measurement in this disease has confirmed that these original observations were largely correct. Clinical studies have demonstrated which patients are at risk of deep vein thrombosis[2,3]. These advances in basic science and technology have led to the development of a number of methods and clinical regimens for the prevention of deep vein thrombosis and pulmonary embolism. These incorporate both pharmacological and physical approaches intended to reduce the coagulability of blood and ensure that venous stasis is avoided[6]. Present prophylactic techniques are based on the model of deep vein thrombosis described in Virchow's triad. The role of anticoagulants in altering the blood coagulation cascade has been studied in detail, and the action of physical agencies in reducing venous stasis has also received attention in scientific investigations over the past four decades[7,8]. The importance of the third component of Virchow's triad, vascular endothelial damage, has not been fully investigated and its role in the development of postoperative deep vein thrombosis is not understood.

Recently Comerota *et al.* have shown that venous distention occurs in upper limb veins during the course of surgical procedures[9,10]. They proposed that this phenomenon may be a significant factor in causing vein wall injury and therefore the initiation of deep venous thrombosis in surgical patients[9]. They have subsequently shown that patients in whom there is distension in the cephalic vein in excess of 20 per cent are at increased risk of postoperative radiofibrinogen-detectable deep vein thrombosis[10]. Support for the role of distension in the pathogenesis of deep vein thrombosis was found by Scurr *et al.* in a clinical study of deep vein thrombosis in surgical patients[11]. The incidence of postoperative deep vein thrombosis was compared in patients receiving intermittent pneumatic compression alone or in combination with graduated compression stockings to prevent thrombosis. The results clearly demonstrated a superior prophylactic effect using both compression methods simultaneously in preventing deep vein thrombosis. It was suggested that vascular endothelial damage, the third component of Virchow's triad, produced by venous distension was prevented by graduated compression stockings but not by intermittent pneumatic compression alone.

The aim of this study was to determine whether the deep veins of the lower extremities dilate during the course of surgery under general anaesthesia.

Patients and methods

Patients undergoing elective surgery at The Middlesex Hospital were entered into this study. Surgical procedures included head and neck, abdominal, and vascular operations, representing a wide range of surgical practice (*Table 1*). Vascular procedures included both abdominal and lower limb arterial reconstructions as well as varicose vein procedures. Only the unoperated limb was included in the analysis for venous distension, to ensure that the operative manipulation had no effect on the limb examined. Patients gave their informed consent for inclusion in the study.

The technique used to measure changes in vein size was high resolution duplex ultrasound imaging. An Acuson 128 (Acuson

Table 1 *Patient population (all subjects)*

	First study	Second study
Mean age (years)	51 (23–75)	47 (22–79)
No. of patients in surgical group		
Head and neck	5	10
Vascular	12	14
Abdominal	14	7
Duration of anaesthesia in min	35 (14–122)	48 (16–183)

Ranges are given in parentheses

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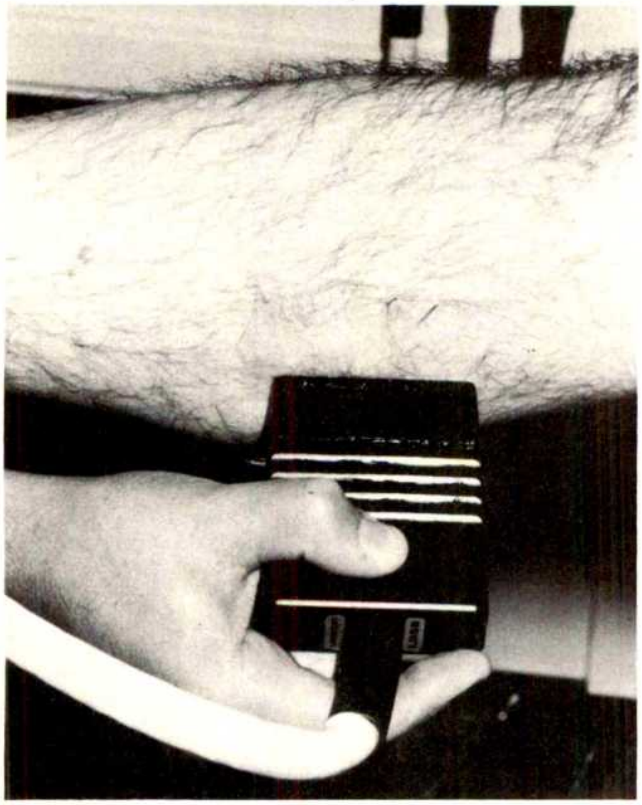

Figure 1 *Scanning technique: high resolution ultrasound imaging was used to measure the diameters of the lower limb veins. The limb was supported by an assistant while images of the gastrocnemius veins were obtained through this medial calf approach*

Incorporated, Mountain View, California, USA) equipped with a 5 MHz linear array transducer was used for all measurements (*Figures 1* and *2*). Longitudinal scans of the legs were obtained because it was found that these data were the most satisfactory for reliable interpretation. It was found that several vein groups could be studied using this technique, and small changes in vein diameter could be detected.

Both lower limbs were studied unless the surgical procedure prevented access to the limb. Images were recorded on videotape for subsequent analysis of vein diameter. The tapes were replayed into an image processing computer (Torch Computers Ltd., Great Shelford, Cambridge, UK). A program written specifically for this purpose by one of the authors (P.D.C-S.) was used to measure the vein diameters, taking into account variations in the scaling of the image. Each vein was measured three times at 5-mm intervals to enable a mean diameter to be calculated. The image processing computer stored these data for subsequent statistical analysis.

The study was conducted in halves. In the first part, patients were scanned and gastrocnemius vein diameters were measured in the medial head of gastrocnemius, immediately below the level of the tibial tuberosity. Vein diameters were measured on three occasions: (1) on the day before surgery, usually the day of admission; (2) after induction of anaesthesia, but before the start of the surgical procedure; and (3) at the end of the surgical procedure, but before recovery from the anaesthetic, with the patient on the operating table.

These intervals were selected to permit an assessment of the effect of anaesthesia on the vein to be tested. The first observation was made with the patient conscious, the last two with the patient anaesthetized. Vein diameters were measured with the patient supine and the limb horizontal and with the limb flexed at right angles, achieved by removing the end of the operating table while an assistant supported the limbs. Patients received peroperative transfusions of intravenous fluids to meet their basal requirements. No specific record of these was kept, although all anaesthesia was supervised by one anaesthetist and conducted using a standard technique.

In the second part of the study the following groups of veins were measured: (1) posterior tibial vein, immediately below the level of the tibial tuberosity; (2) gastrocnemius vein in the medial head of gastrocnemius at the same level; and (3) posterior tibial vein, at the midpoint of the calf. Measurements of vein diameter were made on two occasions: after induction of anaesthesia, but before the start of the surgical procedure; and (2) at the end of the surgical procedure, but before recovery from the anaesthetic, with the patient on the operating table.

In the second part of this study patients were randomly allocated to receive either no additional therapy or intravenous infusion of 1000 ml 0·9 per cent saline in addition to basal requirements during the operative procedure. In patients in whom an intravenous line was inserted to permit access for the administration of anaesthetic agents, 1000 ml 0·9 per cent saline was infused during the course of the surgical procedure. In patients undergoing procedures where fluid infusion was considered necessary or volume replacement was required, 1000 ml 0·9 per cent saline was infused in addition to the calculated basal and transfusion requirements. The purpose of this was to investigate the effect of crystalloid infusion, a factor that may increase the risk of deep vein thrombosis[12]. All patients received appropriate prophylactic treatment to prevent deep vein thrombosis, where indicated. Low-dose subcutaneous heparin was used for this, avoiding compression treatments that might influence venous distension.

For each measurement, ultrasound images of each set of veins were recorded with the patient lying supine on the examination bed or

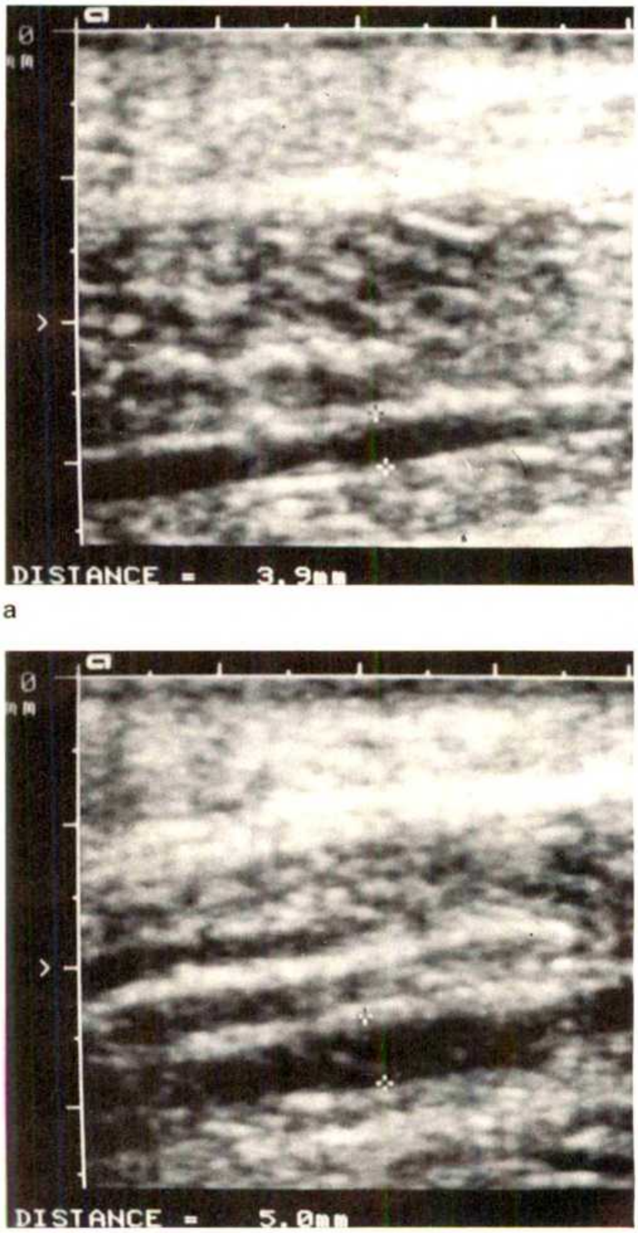

Figure 2 *Longitudinal view of gastrocnemius veins obtained by ultrasound imaging in the supine position at the start* **a** *and end* **b** *of the operation. An increase in the vein diameter can be seen compared with the preoperative views*

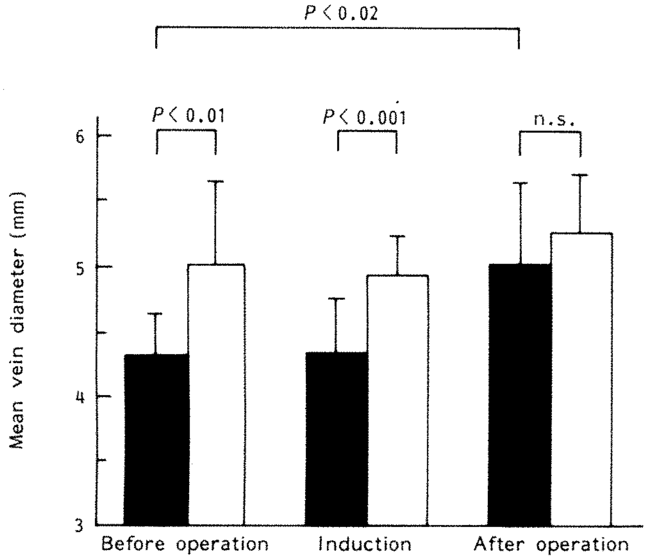

Figure 3 *First study: mean vein diameters of gastrocnemius before, at the start of, and after operation, with the limb supine* (■) *and permitted to hang dependent* (□)*. There is a significant increase in diameter of these veins only at the end of the operative procedure; n.s., not significant*

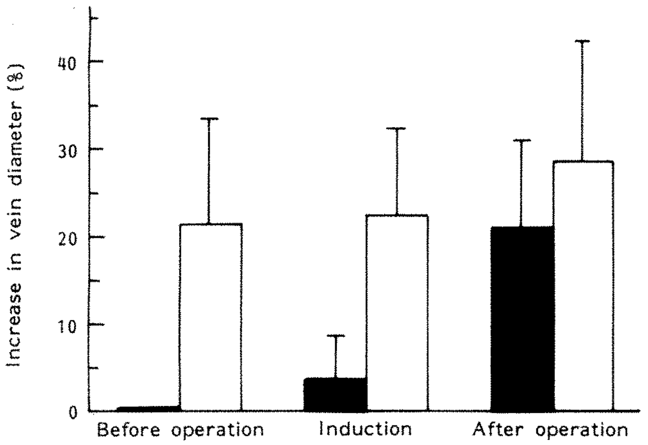

Figure 4 *Percentage increase in vein diameter compared with the supine position before operation in the same patients as in* Figure 3*;* ■*, limb supine;* □*, limb dependent*

operating table. Measurements were then repeated with the knee flexed at right angles. In the operating theatre this was achieved by removing the end of the operating table while the limbs were supported by an assistant. Each limb was then examined in turn, first in the supine position, then with the limb permitted to flex at the knee while the other was maintained supine. The period required to collect the data from each limb for supine and dependent examinations was approximately 1–2 min, as indicated by the time information recorded on videocassette with the ultrasound images. The technique of permitting the limb to hang dependent was used as a means of raising the venous pressure in the leg by a controlled amount, but avoiding the use of a tourniquet. The intention was to assess the distensibility of the veins by this manoeuvre, and was not in any way intended to simulate the normal events during surgery. Since the period of dependency was brief it was assumed that this would not affect the subsequent measurement of vein diameter at the end of the operation.

Statistical analysis of data was undertaken using Student's t test. Paired tests were used for comparison of measurements from the same limb at different times. Two-sample tests were employed to compare values from different patient groups. Pearson's correlation coefficient (r) was calculated to assess correlation between variables. The use of statistical tests that assume a Gaussian distribution of samples was justified by calculating the skewness and kurtosis of the original data. There was no substantial deviation from Gaussian distribution in any of the data analysed. Calculations were made with the assistance of the computer software (SPSSPC, SPSS Incorporated, Chicago, Illinois, USA) running on a microcomputer.

Results

In the first series of observations (*Figure 3*) made only on the gastrocnemius veins, there was no change in the vein diameter immediately after the induction of anaesthesia. The veins retained their ability to distend on dependency and the diameter with the limbs supine was unchanged. It was only at the end of the operative procedure that a statistically significant increase in diameter was observed in the supine position. There was no significant further increase in the diameter of these veins in response to moving to the dependent position, suggesting that they had already become maximally dilated (*Figure 4*).

In the subsequent studies where two sections of the posterior tibial vein were observed in addition to the gastrocnemius veins, the gastrocnemius veins were significantly smaller in diameter than the posterior tibial veins (*Figure 5*). The gastrocnemius veins participate in the calf muscle pump and might be expected to be smaller than the major axial limb vessels. These veins showed a much greater ability to distend in response to a rise in venous pressure than the posterior tibial veins, and this may be in keeping with their pump function. On moving to the dependent position the gastrocnemius veins distended by 37 per cent ($P<0{\cdot}05$) compared with 8 per cent (n.s.) for the midcalf posterior tibial veins. During the operative procedure the mean distension observed in the gastrocnemius veins was 22 per cent ($P<0{\cdot}05$) but vein diameter did not change significantly in either of the posterior tibial measurements.

In the group of patients who received intraoperative saline transfusion the distension was much greater than in the corresponding control group (*Figure 6*). At the end of the operative procedure there was a 48 per cent distension of the gastrocnemius veins in the supine position compared with the preoperative measurement ($P=0{\cdot}003$). This effect was confined to the gastrocnemius veins, and did not reach statistical significance in the posterior tibial veins. The response of the gastrocnemius veins in the control and saline transfusion groups is compared in *Figure 7*.

There was no correlation between the time taken for the surgical procedure and the fractional increase in diameter of the gastrocnemius veins. This did not appear to be a factor in causing augmentation of the distension process in the patients studied.

Discussion

The problem of stasis in the deep veins of the lower extremities during surgical procedures undertaken with general anaesthesia

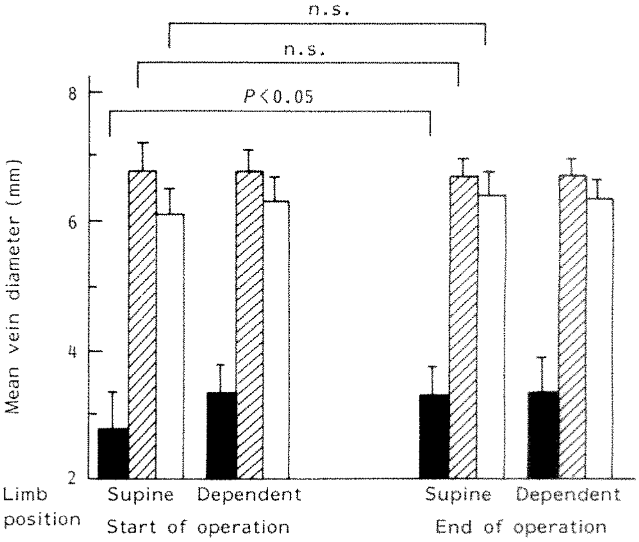

Figure 5 *Second study: venous diameter and response to increased venous pressure in the three veins where measurements were made. Patients are from the control group;* ■*, gastrocnemius;* ▨*, upper posterior tibial veins;* □*, midcalf posterior tibial veins; n.s., not significant*

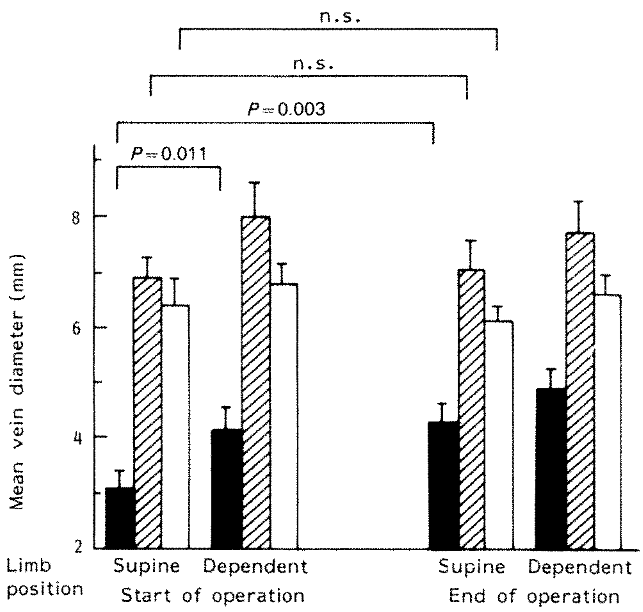

Figure 6 *Second study: the effect of saline transfusion during surgery, comparing the effect on the three sets of veins;* ■, *gastrocnemius,* ▨, *upper posterior tibial veins;* □, *midcalf posterior tibial veins; n.s., not significant*

has been documented in several well controlled independent investigations[13-15]. These experiments have demonstrated the slowing of venous blood flow during anaesthesia, showing both a decrease in blood flow velocity and an increase in the residence time of blood in the deep veins of the calf. This is especially pronounced in the sinuses of the venous valves. A number of factors may result in the stagnation of venous blood in the lower extremities during surgery. The loss of normal muscle tone and hence venous pump function during the course of anaesthesia may result in substantial alterations in the usual flow patterns in the veins of the lower limb, particularly if muscle tone is further reduced by neuromuscular blocking agents[16]. Virchow's triad suggests that stasis in these veins is likely to result in deep vein thrombosis.

The present study provides direct evidence that, concomitant with intraoperative blood flow changes shown by other investigators, there are significant increases in the diameter of the deep veins. We propose that these may lead to the potential for endothelial damage, a further factor suggested by Virchow *et al.* and consistent with recent clinical and ultrastructural studies[11,16]. Of the vessels examined, the gastrocnemius vein appears to undergo the greatest dilatation from induction of anaesthesia to end of operation. However, additional work with the improved scanning capabilities of more recent duplex ultrasound equipment which provides better image resolution is warranted before final comparisons of venous distension at different anatomical sites can be made.

Our findings support the observation of Tripolitis *et al.* that venous capacitance changes in the surgical patient[17]. Our data show that as the venous diameter increases during the operation, the ability to increase further in response to a rise in venous pressure is reduced.

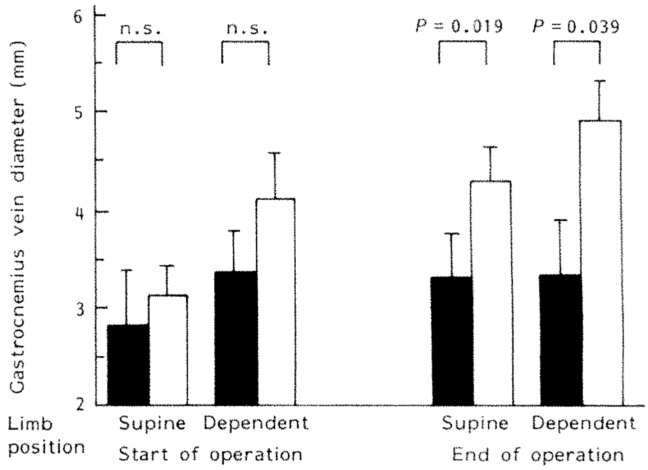

Figure 7 *Second study: response of gastrocnemius veins in the control and saline transfusion groups compared on the same graph. Data are from the same patients as in* Figures 5 *and* 6; ■, *control;* □, *saline transfusion; n.s., not significant*

The effect of saline transfusion on venous distension followed the same trend as in controls, but produced a significantly greater increase in mean vein diameter than in the control group by the end of the operation. This observation suggests that fluid adminstration may be one of the intraoperative factors that resulted in the observed increase in vein diameter in the first study. The relationship between this effect and thrombotic events is not clear from these data, although an association between fluid administration and postoperative deep vein thrombosis has been observed previously[12]. In addition, the roles of graduated elastic compression and intermittent pneumatic compression in providing prophylaxis against deep vein thrombosis are more clearly understood. These findings emphasize the importance of avoiding compression profiles that would tend to trap venous blood in the distal veins when using compression to prevent deep vein thrombosis. This might promote the venous distension that has been observed in this study. Careful application of antiembolism stockings or the use of sequential graduated intermittent pneumatic compression is indicated as the latter has been demonstrated not to trap venous blood distally[18,19].

This study provides direct anatomical evidence demonstrating that events during an operative procedure results in venous distension, in addition to the slowing of flow that previous authors have shown. We suggest that this may contribute to the endothelial damage part of Virchow's triad, promoting the formation of deep vein thrombosis.

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Use of skin graft knife in the treatment of giant perianal condyloma acuminatum

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Epidemiological evidence shows that the incidence of anogenital papilloma virus infection is increasing in the industrial world. Furthermore, such lesions carry a malignant potential for the development of squamous cell carcinoma of the anus[1]. Several methods of treating discrete anogenital condylomata exist. Cytotoxic destruction with podophyllin or related compounds may be effective, although the risk of severe local or systemic side effects is significant. Scissor excision is a simple and effective treatment for all but extensive confluent lesions[2]. However, when the lesions are extensive and confluent, conventional methods of excision cause an unacceptable degree of scarring.

Patients and methods

A modern modification of the Humby skin graft knife is reported in a 53-year-old man with extensive perianal condyloma acuminatum (*Figure 1*). A smaller version of the skin graft knife was necessary for the area near the anal canal (Silver's skin graft knife, incorporating a standard razor blade).

A two-stage excision, with the procedures 1 week apart, was chosen owing to the extent and vascularity of the lesion. Care was taken to preserve part of the dermis, and no skin graft was necessary. The patient was discharged on the fifth postoperative day. Two further excisions of small discrete lesions were performed at 8 and 17 months. An excellent functional and cosmetic result was achieved (*Figure 2*).

Results

The histological appearances were those of a giant condyloma acuminatum with Grade II intraepithelial neoplasia. There was no evidence of invasive squamous carcinoma. It did not represent a Buschke–Loewenstein tumour.

In situ hybridization for human papillomavirus was performed on representative paraffin blocks[3], and positive signals were found for human papillomavirus (HPV) types 6 and 11. Benign anogenital condylomata consistently show HPV 6 and/or 11, whereas malignant transformation appears to be associated with HPV 16 and 18 (Reference 3).

Discussion

If skin graft knife excision of an extensive perianal condyloma is contemplated, a staged excision is preferable. The lesion in this patient was very vascular, and significant blood loss was encountered. A smaller skin graft knife is useful for that part of the lesion near the anal canal, where access may be difficult.

A paraffin gauze dressing was satisfactory in the postoperative period. The patient was encouraged to have daily baths.

The use of a skin graft knife has provided a simple, effective method of excision of this extensive lesion, giving an excellent functional and cosmetic result.

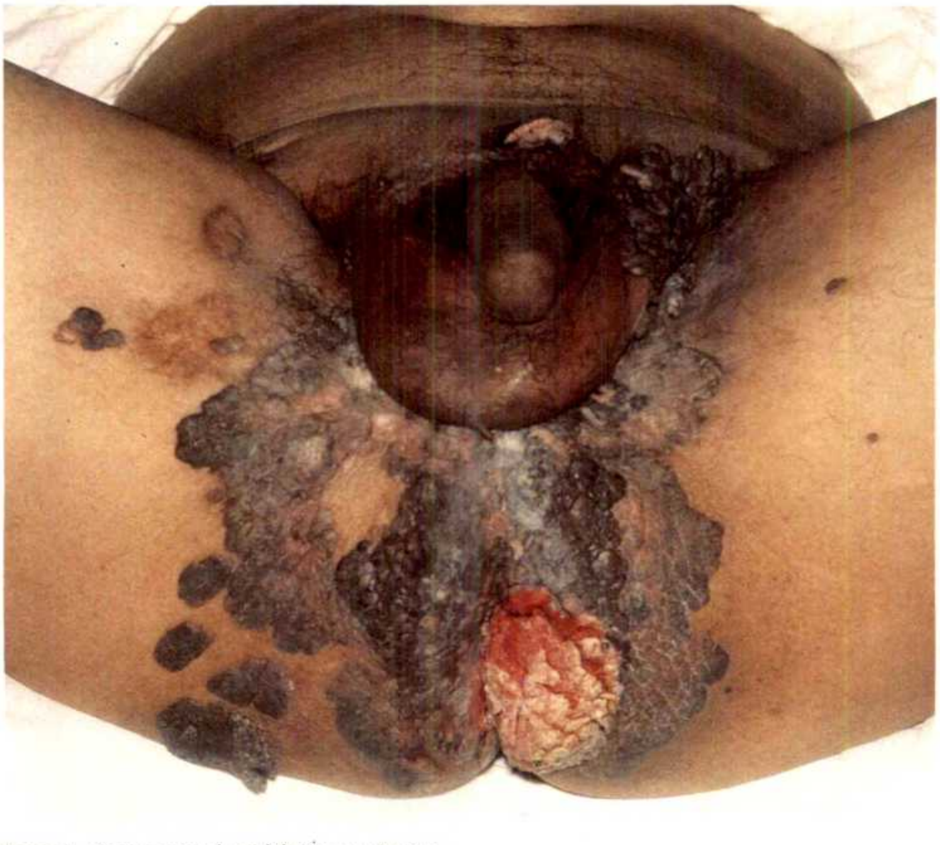

Figure 1 *Giant perianal condyloma acuminatum*

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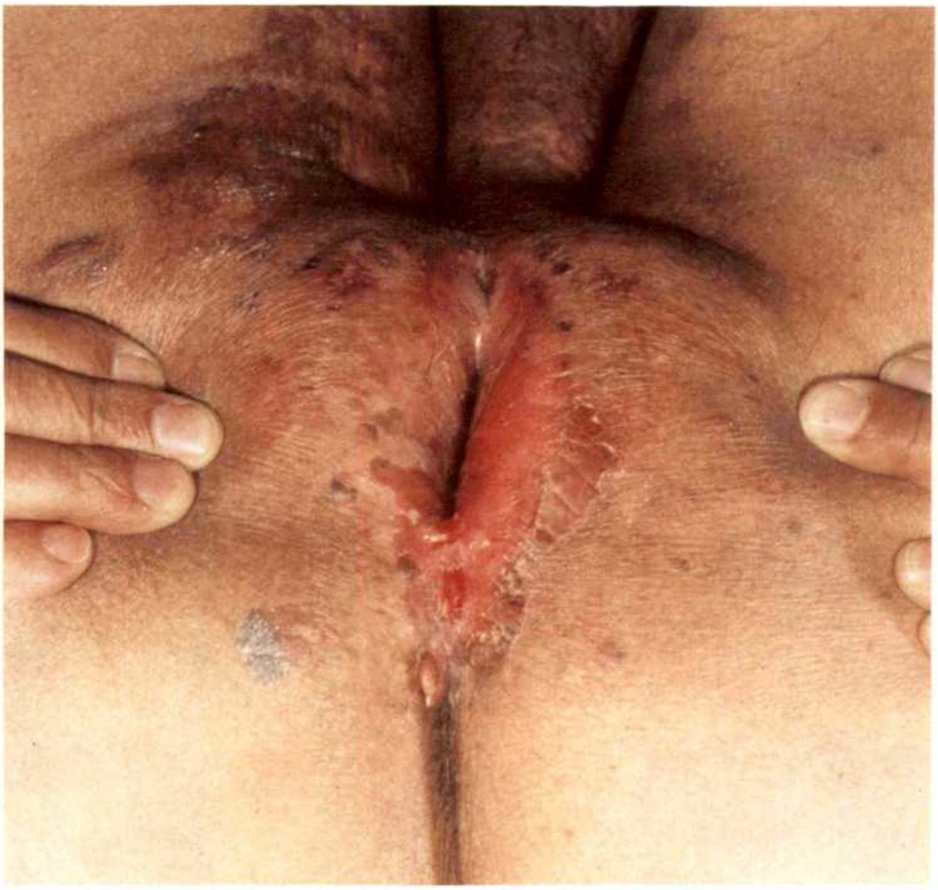

Figure 2 *Sixteen months after excision with skin graft knife. A few localized recurrences were subsequently excised*

Acknowledgements

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Percutaneous gastrostomy: an alternative endoscopic approach

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Improvements in upper gastrointestinal endoscopy have led to the development of percutaneous gastrostomy performed under light sedation[1]. This technique is now widely used and has few complications[2]. A new endoscopy-assisted technique for insertion of a percutaneous gastrostomy tube using the Nottingham trocar and sheath (Add-A-Cath, Femcare Ltd., Nottingham, UK) which was originally designed for suprapubic catheterization[3] is described.

Technique

The patient is positioned supine on a trolley and sedated with intravenous diazepam (Diazemuls®, KabiVitrum, Uxbridge, UK) 5–20 mg. The skin is cleaned and the area draped. A single dose of a broad-spectrum antibiotic is given intravenously. An upper gastrointestinal endoscopy is performed to inflate the stomach and to exclude any contraindication to percutaneous gastrostomy. The light from the endoscope is visualized through the anterior abdominal wall and a point in the midline or left hypochondrium above the light is selected and infiltrated with 5 ml 1 per cent lignocaine. A small incision is made in the skin and subcutaneous tissue at the proposed site of gastrostomy.

The Nottingham trocar and sheath, which consists of a central trocar with a sharp tip and outer sheath with pull tab and tear-off strip, is inserted through the incision into the peritoneal cavity. The sheath alone is then advanced until its indentation on the gastric wall is confirmed by the endoscopist. Once the position of the sheath is satisfactory the trocar is advanced and both are inserted into the stomach. Entry into the stomach is confirmed endoscopically (*Figure 1*). A 16 Fr silicon catheter is then introduced into the stomach via the sheath and its balloon is inflated with 10 ml normal saline. The sheath is withdrawn and peeled off (*Figure 2*). The catheter is secured with a 2/0 silk suture after it has been pulled to appose the gastric wall to the anterior abdominal wall.

Results

To date this technique has been used successfully in eight patients with neurological dysphagia and there have been no significant complications. In two other patients the procedure was abandoned because adequate endoscopy was impossible.

The eight patients with gastrostomies were discharged home and have managed without problems for a median of 180 days (range 30–300 days). Three patients had their gastrostomy catheters changed without incident.

Discussion

This technique has the advantage of simplicity. There is less manipulation of equipment than with either the 'pull' technique where the feeding catheter is 'railroaded' down through the mouth[4], or the 'introducer' method where dilatation of the entry track is required[5].

Minor complications such as leakage of gastric contents, blockage of the catheter or peritubal skin infections have not been encountered and damage to the posterior gastric wall can be avoided by good communication between the endoscopist and the operator. Despite the alternatives of fine-bore feeding tubes and parenteral nutrition, gastrostomy retains a valuable role in patients with chronic disease affecting the pharynx or oesophagus. It is concluded that the Nottingham trocar and sheath affords a simple, effective and safe means of inserting a gastrostomy tube.

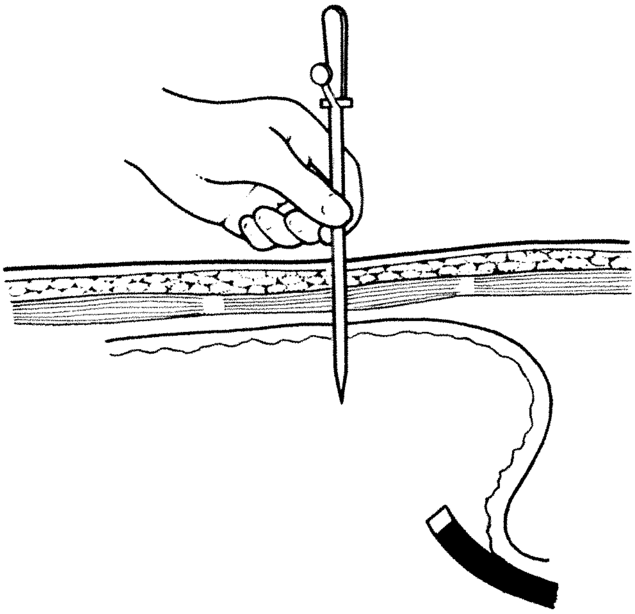

Figure 1 *Insertion of trocar and sheath*

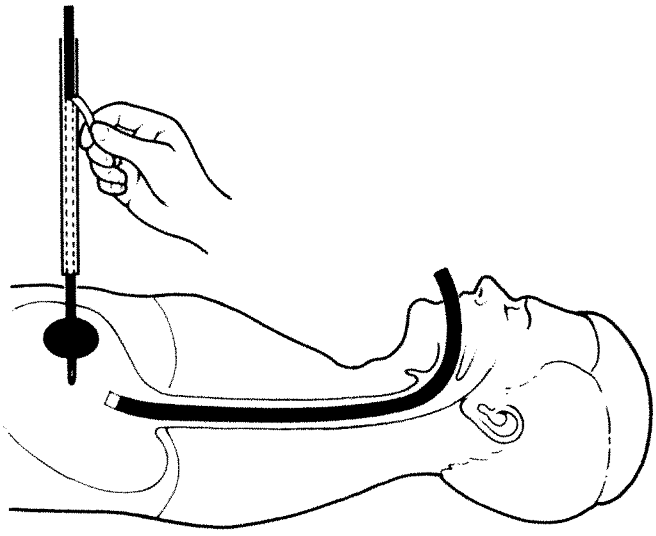

Figure 2 *The peeling off technique allowing the sheath to be removed*

Acknowledgements

We wish to thank the endoscopy staff of University and City Hospitals, Nottingham for their invaluable assistance.

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For debate

Cancer of the colon and rectum

The seventh King's Fund Forum was held in London from 18–20 June 1990. A panel of twelve listened to evidence from experts in public sessions attended by professionals from many fields as well as the public and press.

Consensus statement

Last year 22 000 people died of cancer of the colon and rectum in Britain and, of those diagnosed in 1990, less than 30 per cent will survive 5 years. Cancer of the colon and rectum is the second most frequent cause of cancer death in Britain and the West. In the past 20 years, treatment has had little impact on the survival. It is a disease of older people and the numbers of new cases and deaths will continue to increase with the growing numbers of the elderly. There is little public recognition of the fact that in Britain today there may be over a quarter of a million people living with cancer of the large bowel. This may partly be due to the stigma and embarrassment of bowel cancer. Some patients delay seeking help through fear and ignorance. Others require major emergency surgery for which they are totally unprepared. Knowledge about this cancer has remained more in the medical domain than, for instance, breast cancer. This consensus statement is made to raise public awareness of this common and often devastating disease.

The panel was asked to address the following questions:

1. Would the detection and treatment of polyps reduce the incidence of cancer of the colon and rectum?

It is important to define a number of terms before discussing prevention and management. Most polyps and all colorectal cancers are neoplasms or new growths. Cancer is diagnosed histologically when the growth invades locally through the inner lining of the bowel. A more precise term for a neoplastic polyp is an adenoma. Three types of adenoma can be defined by the pathologist: tubular, tubulovillous and villous, of which the latter is thought to have the greatest invasive potential.

Whether or not the detection of polyps would reduce the incidence of cancer of the colon and rectum depends upon the premise that most colorectal cancers develop from adenomatous polyps. There is now a great deal of circumstantial evidence to support the polyp–cancer sequence although alternative mechanisms may account for the carcinomas which arise in patients with longstanding ulcerative colitis and the rare cancers which arise apparently *de novo*.

When the adenoma–carcinoma sequence was first proposed the evidence originated from epidemiological and clinical studies For example, in countries with a low prevalence of adenomas the incidence of colorectal carcinoma is low. Studies of patients with the genetic condition familial adenomatous polyposis, in which affected individuals have multiple large bowel tubular adenomas and a high risk of colorectal cancer, support this hypothesis. Recent molecular genetic studies have added strong evidence for the concept of the adenoma–carcinoma sequence.

If the great majority of cancers develop within an adenoma, it follows that detection and removal of adenomatous polyps in asymptomatic individuals should theoretically reduce cancer incidence and mortality. The problem is that autopsy studies have shown adenomas to be far more prevalent than carcinomas (30 per cent compared to 2 per cent). Double contrast barium enema will diagnose polyps, but the most reliable diagnostic technique for the detection of adenomas is colonoscopy. However, it is invasive and there are no good colonoscopic indicators of malignant potential other than size. **There is therefore no case for colonoscopic screening on a population basis.**

Evidence from occult blood screening of asymptomatic populations suggests that it may detect the larger and more friable adenomas with a higher risk of malignant change, but at present no judgement can be made on whether this confers survival benefit. The results of the European randomized controlled trials for screening will consider this question and may provide evidence as to whether the smaller adenoma detected by the screening method presents as a cancer at a later screening round or as an interval cancer (i.e. presenting between screening rounds).

We recommend that: **The use of colonoscopy in the asymptomatic individual is justified only in those with a high genetic risk of developing cancer and in the follow-up of some of those patients who have had a symptomatic adenoma previously removed endoscopically.**

In the symptomatic patient with a polyp, the whole of the large bowel is examined and polyps greater than 5 mm in diameter removed. The management of polyps less than 5 mm is a problem which will be resolved only by more studies of their natural history.

It is uncertain which patients require follow up after removal of symptomatic polyps and how often. Development of new (metachronous) adenomas is variable and information regarding this comes mainly from retrospective surgical, and only a limited number of prospective, studies. Follow-up is not indicated for patients with a single small tubular rectal adenoma and those over the age of 75 years. Those individuals with a large adenoma or any type of multiple adenomas should undergo colonoscopic surveillance at 3–5-yearly intervals. The risks of colonoscopy are small but real and can be minimized by an expert colonoscopist.

In order to deal adequately with the existing demands of symptomatic individuals and screening of high risk groups, provision for colonoscopic services, including training, needs to be improved.

2. What preventative measures are there which will safely reduce the incidence and mortality of cancer of the colon and rectum?

Reduction in incidence and mortality may be achieved by reducing exposure to causative factors such as diet, or by detecting the condition at a premalignant stage through screening

Diet

The wide geographical variations in colorectal cancer incidence suggest a strong environmental influence and this is confirmed by studies of migrant groups Interest in dietary aetiology began with the hypothesis that the higher fibre intake of low incidence populations protected them against colorectal cancer. There are great methodological difficulties in studying the association between diet and cancer. Most of the epidemiological evidence is weak, based mainly on correlations at a population level and a small number of case-control studies It is necessary to be cautious about generalizing from animal studies.

A dietary aetiology is plausible because diet has been shown to have an important influence on bowel function and metabolism. So far, the main factors linked with increased colorectal cancer have been high intakes of fat and energy and low intakes of fruit and vegetable fibre. Cereal fibre does not appear to provide any protection against colorectal cancer

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Although there is a general view that diet is probably the most important environmental cause of colorectal cancer **the evidence is not strong enough to recommend dietary changes.** However, a reduction in fat and energy intake and an increase in fruit and vegetable fibre would be in line with recommendations for dietary change relating to other diseases.

Screening

It has been suggested that screening may decrease morbidity and mortality of colorectal cancer by the detection of early cancers in high risk groups and the population.

Population screening. Rectal examination, sigmoidoscopy and faecal occult blood testing have all been suggested as methods of screening asymptomatic populations The first two are impracticable as screening tools and would detect only a small proportion of distal cancers Faecal occult blood testing is non-invasive but has problems of limited specificity and sensitivity and is taken up by around 60 per cent of those offered it.

Because of various biases the efficacy of screening must be evaluated by randomized controlled trials. Results from trials suggest that cancers detected in the screened population are more likely to be at an early stage than cancers presenting in an unscreened population, and that a higher proportion can be dealt with endoscopically than surgically. However, it is not known whether screening will significantly improve the duration or quality of life in a population offered screening compared with a population not offered screening. Any decision on a screening programme must take account of all the costs, including the foregone benefits of displaced alternative projects. In addition to the effects on health service costs, the costs to patients and their families must be considered, taking into account unnecessary anxiety and the risks of complications of colonoscopy for false positives. In the event that screening is introduced, it will be necessary to ensure that there are additional diagnostic facilities available to meet the demand for additional tests generated by the programme. It will also be important that people offered screening are told about the implications of the different outcomes of the tests. A large study of faecal occult blood screening is currently in progress in Nottingham, UK and its results are expected in 1995. **It is recommended that no decision on the introduction of faecal occult blood population screening is made before 1995.**

Screening of high risk groups In individuals with a high genetic risk of developing adenomas and/or carcinomas the balance of the benefit of screening in relation to risks and costs is more favourable than for the general population. Response and detection rates are improved and invasive procedures may be justified.

Those at highest genetic risk are the offspring of individuals with familial adenomatous polyposis and the two hereditary non-polyposis colorectal cancer syndromes. These conditions are autosomal dominantly inherited and are estimated to account for 0·5–1 per cent and 5–10 per cent of all colorectal cancers respectively. The diagnosis of familial adenomatous polyposis (FAP) is straightforward although clinicians should be aware that 30 per cent of people presenting may have no family history. The clinician should be alerted to the possibility of the hereditary non-polyposis syndromes by the occurrence of colorectal cancer in young people and particularly where the lesion is right-sided. Affected relatives may be identified in the family with either colorectal disease or adenocarcinoma elsewhere (e.g. breast, uterus, ovary).

There is a significantly increased frequency of colorectal cancer in first degree relatives of people with colorectal cancer The empiric risk of developing cancer varies from 1:17 for individuals with one first degree relative affected to 1:6 with two first degree relatives. **It is recommended that a comprehensive family history is taken as part of the assessment of all individuals with colorectal cancer.**

Those families in which a significant genetic risk is suspected should be referred for genetic counselling and accurate risk determination. **It is recommended that, given the number of people involved and the resource consequences, such screening must be evaluated.**

Recent advances in molecular biology mean that there is the potential to use linked DNA markers in FAP families to determine genetic risk, thus confining the need for regular colonoscopic surveillance to those family members at high risk. Markers for other dominant syndromes may be available in the near future.

Case finding. This is the identification of affected but asymptomatic individuals by opportunistic screening, for example when a patient presents to the general practitioner with an unrelated condition In the absence of an adequately evaluated non-invasive screening method, case finding cannot be recommended. However, the taking of a good family history is essential as it may identify a high risk individual who should be referred for further investigation.

Assessment of the symptomatic patient. Patients with colorectal cancers usually present to their general practitioner with non-specific gastrointestinal symptoms. Delay in referral and diagnosis may influence outcome. Abdominal and rectal examinations are essential to determine the urgency of referral. There is evidence that they are not performed on a large proportion of patients who are subsequently found to have colorectal cancer. **Faecal occult blood testing is of no value in the assessment of the symptomatic patient in general practice because of its low specificity and sensitivity.**

3. How effective are current treatments for cancer of the colon and rectum at improving survival and quality of life?

The efficacy of treatment is limited. Survival and quality of life after treatment for colorectal cancer will vary according to the individual patient, the site and stage of the tumour, its presentation, its treatment as an emergency or an elective case, and between hospitals Increasingly, treatment involves a number of disciplines and a team approach is essential.

Surgery

Most patients referred to hospital will first be seen by a surgeon. There is good evidence that variations in operative mortality, postoperative morbidity and survival are all surgeon related. The skill and training of the operating surgeon has a crucial effect on outcome. This particularly applies to rectal surgery, in which major procedures carry a significant risk of damage to nerves supplying the bladder and sexual organs. There is no formal organization for colorectal surgery in the United Kingdom, and it is not yet recognized as a separate subspecialty. **It is recommended that each district should have at least one colorectal surgeon.** Failing this, colorectal cancer patients should be referred to another hospital which does have a specialist; even then local surgeons should be organized so that one surgeon can assume responsibility for colorectal cancer. **Proper local referral and treatment protocols should be developed for both elective and emergency colorectal surgery.**

Advanced surgical techniques, encouraged by specialization, have reduced the need for a permanent colostomy but, despite this increasing trend, some patients are treated with a colostomy unnecessarily. Tumours close to the anal canal still have to be treated by excision of the rectum and a colostomy **Those patients who do require a temporary or permanent colostomy will continue to need the support of specialist stoma nurses.** Their extended role will include both information on new appliances and techniques and counselling before and after surgery.

Pathology

The accurate reporting of histopathology on resection and polypectomy specimens is time consuming but essential for the assessment of prognosis and further treatment. **Standards of reporting have recently been outlined by the United Kingdom Central Committee for Cancer Research (UKCCCR) and should be followed.** Adequate support, staff and resources must be provided for this important task.

Radiotherapy

For rectal cancer preoperative radiotherapy reduces the incidence of local recurrence, but some early cancers may be treated unnecessarily. Similar benefit accrues from radiotherapy given postoperatively; postoperative assessment permits the selection of those patients with later stage disease. There is however a greater risk of side effects. Although radiotherapy helps to prevent recurrence there is no evidence that it prolongs survival. Palliative radiotherapy may have a useful role in patients with established disease, particularly in the pelvis.

Chemotherapy

Adjuvant chemotherapy (i.e given at the time of surgery) aims to control the metastatic potential of a tumour Up to 25 per cent of patients with colorectal cancer develop liver metastases. The recently introduced AXIS national trial of adjuvant chemotherapy and radiotherapy is assessing the effect of 5-fluorouracil (5FU) infusion into the portal vein. **It is recommended that surgeons enter suitable patients into the AXIS national trials.**

Recent evidence suggests that patients with advanced (Dukes' C) colon tumours may be improved by adjuvant therapy with 5FU and levamisole, and such patients not entered into trials should be considered for this treatment

Studies in advanced colorectal cancer treated with 5FU and folinic acid show some value and may be effective as palliation in patients with advanced disease

Other palliative treatments

Older patients who are frail and might otherwise have a colostomy or major resection with a high mortality rate can be treated by laser therapy or transanal resection to reduce distressing symptoms In carefully selected cases, partial liver resections for one or two metastases confined to a single lobe of the liver may prolong survival and offer useful palliation. General palliative care is important.

Follow-up

Arrangements for follow-up are haphazard and poorly organized The aims of follow-up are the detection of overlooked synchronous tumours, the detection of recurrent cancer and new tumours at an early stage, patient support, and the audit of results. **Follow-up is expensive and studies of its efficacy, organization, frequency and new methods of detection are needed.** For example, the use of the tumour marker CEA (carcinoembryonic antigen) as an indicator of local recurrence is being assessed, and optimal postoperative colonoscopy screening intervals need to be determined. Colorectal specialization would encourage the inclusion of patients in trials with systematic follow-up protocols

Measuring outcome

The standard medical assessment of outcome that concentrates on survival, disease free interval and recurrence may under- or over-estimate the benefit of treatment. Patients however are extremely concerned about the quality not just the quantity of life. Valid standardized tests of quality of life which assess the impact of treatment on psychological, social, occupational and sexual function are available and have proved useful in the treatment of other types of cancer. **These tests have not been used in trials of colorectal cancer therapy, and must be used routinely in the future.**

Better information

There is widespread ignorance about colorectal anatomy, function, disease and treatment Good information about services, treatment outcomes and quality of care is essential if patients are to be able to make informed choices. The full range of cancer information agencies has an important part to play. As quality assurance prompts hospitals to publish results of treatments and outcomes, patients and their general practitioners will begin to change referral patterns which could reinforce specialization. **It is critical that measures of outcome are properly audited, and made available to the general public.**

Regional cancer registries provide invaluable information and should be supported.

4. What is the direction for future research?

Research

There are gaps in our knowledge about the natural history of colorectal cancer and the effects of treatment At present only 2 per cent of colorectal cancer patients are entered into clinical trials. The resource implications of new screening or treatment approaches must be carefully considered In addition to those areas already highlighted **it is recommended that research efforts be directed towards the following:**

1. The natural history of the adenoma, dysplasia and cancer,and the effects of intervention.
2. The molecular biology of colorectal cancer.
3. Hereditary factors – the evaluation of the practical and social implications of surveillance of high risk families.
4. The development of more sensitive tests of the physical and biological activity of tumours in order to facilitate the accurate pre- and post-operative staging of colorectal cancer.
5. The development of new treatments to improve survival and quality of life.
6. The use of validated quality of life measures in all clinical trials of colorectal cancer therapy.
7. Studies which will provide insights into the patients' experience of colorectal cancer, its treatment and the impact on their lives.

One copy of the consensus statement is available free of charge on request from: The King's Fund Forum, King's Fund Centre, 126 Albert Street, London NW1 7NF. Tel: 071 267 6111 Ext. 209 Extra copies may be purchased at 40p per copy

Acknowledgements

The panel comprised: Professor R Anderson (Chair), Dr P. Alderson, Professor T. Cooke, Dr A Davison, Dr L. Fallowfield, Mr H. Gravelle, Dr S. Huson, Dr M Lloyd, Dr K. Melia, Mr N. Mortensen, Dr R. Newcombe and Ms F. Winkler.

Invited experts presenting evidence were: Dr S. Ahmedzai, Mr R. Akehurst, Dr S. Arnott, Dr R Begent, Dr S Bingham, Dr P. Boyle, Dr H. Cuckle, Dr T Davies, Professor Sir Richard Doll, Mr M. Dunlop, Professor J. Hardcastle, Dr M Hill, Dr V. Murday, Mrs C. Myers, Mr G Oates, Mr R Phillips, Dr P. Quirke, Mr M. Rees, Mr W Reynolds, Dr P. Skrabanek, Professor I Taylor, Professor N. Wald, Mr A. Walker, Dr C Williams, Professor N. Wright

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Human Kupffer cells are cytotoxic against human colon adenocarcinoma

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Colorectal liver metastases are a common clinical problem and require more effective therapy. Kupffer cells (KC) perform many important homeostatic functions within the liver and may also possess the ability to mediate tumor cytotoxicity. We investigated the ability of human KC to mediate cytotoxicity against human colon adenocarcinoma targets (HT 29) in vitro Unstimulated human KC were cytotoxic against the HT 29 targets at all effector/target ratios tested. This cytotoxicity was increased significantly ($p < 0.05$) when the KC were stimulated with interferon-γ and lipopolysaccharide. Human KC produced tumor necrosis factor (TNF), and KC stimulation significantly ($p < 0.05$) increased secretion of this monokine. The addition of anti-TNF antibody to the KC-HT 29 cocultures completely neutralized all of the available TNF yet cytotoxicity was not affected, suggesting the participation of a membrane-bound form of TNF or other mechanisms. (SURGERY 1990;108:400-5.)

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THE LIVER IS A COMMON site of metastatic spread, and current therapy remains ineffective in treating this disease. Little is known about the mechanisms responsible for controlling growth and development of liver metastases. Through an understanding of these mechanisms, new and improved strategies to treat liver metastases can be developed.

Initial investigations with a syngeneic mouse tumor model of colorectal liver metastases have demonstrated that murine Kupffer cells (KC) play an important role in controlling the growth and development of liver metastases.[1] One prominent effector mechanism of the murine KC is dependent on tumor necrosis factor (TNF), although other mechanisms may also be operant.[2] Based on this work in the mouse, we have speculated that human KC may also display cytotoxic activity against human colon tumor cell lines. Hopefully, through an understanding of the cytotoxic mechanisms of human KC, strategies to stimulate human KC to prevent or eradicate hepatic metastases can be developed rationally.

The aim of this investigation is to determine if (1) human KC are cytotoxic against human colon carcinoma in vitro, (2) this cytotoxic activity can be stimulated, and (3) human KC mediate cytotoxicity through the secretion of TNF.

MATERIAL AND METHODS

Isolation of human KC. At the time of resection for colon cancer in six patients, a small (2 × 2 cm) wedge biopsy specimen of the liver was obtained. The specimen was placed in an enzyme solution (0.05% collagenase and deoxyribonuclease) and incubated in a shaking water bath at 37° C for 35 minutes. The cell suspension in Dulbecco's phosphate-buffered saline solution (DPBS) was placed on a 30% metrizamide gradient and centrifuged for 20 minutes (1400 *g* at 4° C). The KC were taken from the metrizamide-DPBS interface, washed, and placed in a 96-microwell plate at various effector concentrations (0.5×10^5, 1.0×10^5, and 2.5×10^5 KC/well). The KC adhered for 2 hours and were washed twice with DPBS. This technique produced a suspension of >95% KC as determined by (1) macrophage morphology in a Wright-Giemsa–stained

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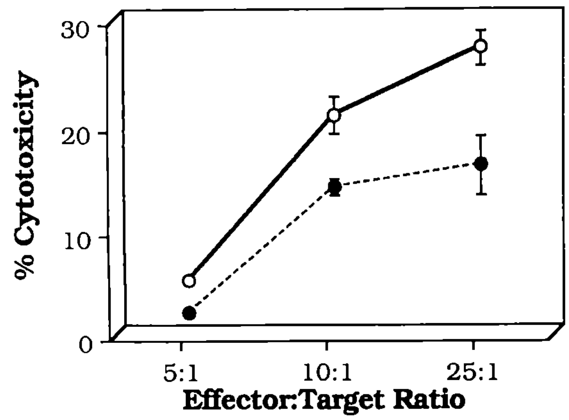

Fig. 1. Human ($n = 6$) KC cytotoxic activity against ^{125}IUdR-labeled human HT 29 colon adenocarcinoma target cell line. The KC were activated with 100 units/ml of IFN-γ and 100 ng/ml of LPS. O——O, Stimulated KC; ●——●, unstimulated KC

cytospin preparation, (2) phagocytic uptake of colloidal carbon, and (3) positive α-naphthylacetate staining.

All reagents and media were screened before use and contained ≤ 0.01 ng/ml of endotoxin by the limulus amoebocyte assay (Cape Cod Associates, Woods Hole, Mass.).

Target labeling. The HT 29 human colon adenocarcinoma targets were provided by Dr. Isaiah J. Fidler, Department of Cell Biology, MD Anderson Cancer Center The targets (3×10^5 cells/ml) were labeled with 0.2 μCi/ml iodine 125-labeled idoxuridine (^{125}IUdR) for 18 hours At the completion of this incubation, the labeled cells were washed three times with tissue culture medium (RPMI 1640), resuspended in the same medium, and incubated for 3 to 4 hours at 37° C to allow nonincorporated label to be released into the supernatant (cold chase). After the cold chase, the cells were centrifuged and resuspended to a concentration of 2.5×10^6 viable cells/ml by the addition of tissue culture medium The cell viability was at least 90% as determined by trypan blue exclusion. Spontaneous release of ^{125}I from the HT 29-labeled targets at 24 hours was 8% and increased to 25% at 72 hours.

KC cytotoxicity assay. One hundred microliters of labeled (1×10^4 cells/well) targets was added to flat-bottom microtiter plates (Linbro Scientific, Hamden, Conn.) containing KC to give effector/target ratios of 5:1, 10·1, and 25.1. Control wells containing only target cells were used to monitor spontaneous release of the radiolabel. The cells were incubated for 72 hours at 37° C in an atmosphere of 5% CO_2 and air. To terminate the assay, the plates were spun at 100 *g* for 5 minutes at 4° C. Triplicate 100 μl samples of the supernatant were removed from each well and counted in a Packard γ-counter with the ^{125}I window. Total label was determined by counting an aliquot of input-labeled targets. Cytotoxicity was quantified by the following equation: % Cytotoxicity = [cpm experimental − cpm spontaneous release/cpm total − cpm spontaneous release] × 100.

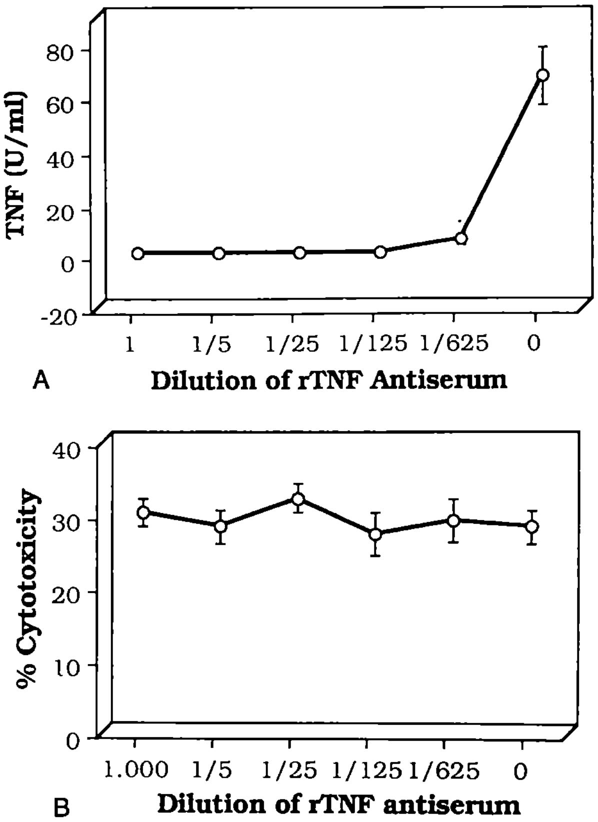

Fig. 2. A, Effect of anti-human TNF antibody on the biologic activity of soluble TNF. Various dilutions of anti-TNF antiserum were added to activated KC cultures and the cell-free supernatants were analyzed for TNF at 24 hours The 0 value represents no antiserum. **B**, Effect of antihuman TNF antibody on KC cytotoxicity against ^{125}IUdR-labeled HT 29 targets. Anti-TNF antiserum was added at the same dilutions as in *A* to cultures of activated KC and ^{125}IUdR-labeled HT 29 targets Cytotoxicity was measured after 72 hours

In certain experiments the KC were activated with a two-signal sequence. The first signal (priming) was a 1-hour incubation with recombinant human interferon-γ (IFN-γ). The second signal (triggering) was the addition of 100 ng/ml of lipopolysaccharide (LPS).

TNF biologic assay. The TNF activity in the culture supernatants of KC was determined in a biologic assay with actinomycin D-treated L929 cells [3] Then 15×10^3 L929 cells were seeded in 150 μl of tissue culture medium in 0 33 cm^2 wells of 96-well plates After an over-

Table I. TNF production by human Kupffer cells

Effector cell	*TNF (units)*
Unstimulated KC	25.3 ± 2.0
Stimulated KC	43.6 ± 1.6*

*$p < 0.05$, stimulated versus unstimulated

night incubation, 50 μl of medium containing 4 μg/ml actinomycin D was added to the cells, and 100 μl of the test supernatants was titered 1:3 in replicate on these targets. After an additional 18 to 24 hours of incubation, the remaining viable cells were stained for 1 hour with neutral red; free stain was removed by washing and incorporated stain was resolubilized with acidified ethanol. The optical density at 540 nm in each well was determined in a plate-reader apparatus. The titer corresponding to 50% inhibition of neutral red incorporation (1 unit) was determined by linear regression.

In selected experiments, KC-HT 29 cocultures were established in the presence of a dose range of immunoglobulin isolated from rabbit antiserum raised against recombinant human TNF. This globulin fraction was isolated by affinity chromatography on protein A-Sepharose. The antibody concentration designated *1* in Fig. 2 represents a concentration of ~4% to 5% of that in the original serum. At the termination of the 72-hour coculture, the supernatants were assayed for ^{125}I released from target cells and for TNF released by the KC.

Statistical analysis. The paired Student *t* test has been used for all statistical analyses.

RESULTS

The initial set of experiments tested the cytotoxic function of human KC against a human colon adenocarcinoma (HT 29) cell line. KC (at effector/target ratios of 5:1, 10:1, and 25:1) were cocultured with ^{125}IUdR-labeled HT 29 targets for 72 hours. At the completion of this incubation, cytotoxicity against the labeled targets was measured (Fig. 1) These results demonstrate that (1) unstimulated or resident KC were inherently cytotoxic against human colon adenocarcinoma in a density-dependent manner and (2) KC cytotoxic function could be significantly ($p < 0.05$) increased by activating the KC (at the 10:1 and 25:1 effector/target ratios).

The next experiment investigated whether human KC mediated cytotoxicity through the secretion of TNF—a prominent effector mechanism in murine KC cytotoxicity. The cell-free supernatants from unstimulated and activated KC were collected after a 72-hour incubation and analyzed for soluble TNF (Table I). These results have demonstrated that (1) human KC produced TNF and (2) activated KC produced a significantly ($p < 0.05$) greater amount of TNF than did unstimulated KC. However, demonstrating production of TNF did not prove that this was the effector mechanism mediating cytolysis of HT 29 targets.

The next experiment investigated whether TNF mediated human KC cytotoxicity against the HT 29 targets. Anti-TNF antibody (at various dilutions) was added to the KC-HT 29 coculture (effector/target ratio, 25:1) for a 72-hour assay. At the completion of the incubation, the cell-free supernatants were analyzed for (1) the quantity of soluble TNF (Fig. 2, *A*), and (2) release of radiolabel from the targets (Fig. 2, *B*). In this manner a correlation could be made between the quantity of available TNF and the level of KC cytotoxicity against the targets.

These results demonstrated that (1) the TNF antibody (at all dilutions) neutralized all of the available TNF and (2) the absence of TNF did not affect KC cytotoxicity against the HT 29 targets. By comparing the inhibitory effects on direct cell lysis and soluble TNF at identical levels of antibody, it is clear that lysis can proceed effectively in the absence of soluble TNF. These results suggest that either (1) the cytotoxic mechanism is TNF independent or (2) it depends on a membrane TNF that is difficult to neutralize with this antibody under these conditions. The latter model has recently been reported in murine macrophage tumor cytotoxicity.[4]

These initial results have demonstrated that (1) human KC are cytotoxic against the human colon adenocarcinoma cell line in vitro, (2) this cytotoxic function can be stimulated significantly in vitro, (3) human KC produce TNF, and (4) human KC exert cytotoxic activity through a mechanism that is independent of soluble TNF.

DISCUSSION

More than 155,000 new cases of colorectal cancer are diagnosed each year in the United States and account for 60,000 deaths.[5] Liver metastases are present in 20% to 25% of patients at the time of initial diagnosis of the colon cancer and will ultimately develop in two thirds of patients with colorectal cancer.[6] The overall prognosis is poor, with several large series reporting survival rates of 4 to 8 months.[7-9] Despite various forms of therapy, the majority of patients are dead within 2 years from the time of diagnosis. More effective therapy must be developed to treat this frequent and lethal complication of cancer.

The liver performs many diverse functions ranging from biotransformation of xenobiotic pollutants and endogenous metabolites to phagocytic removal of bacteria and other particulate matter from the circulation. Potentially the liver may also possess effector populations that have the inherent ability to destroy tumor cells.

Our initial studies in the mouse have indicated that macrophages regulate the development of in vivo liver metastases from a murine colon adenocarcinoma cell line (MCA 26).[1] This work has demonstrated that the in vivo modulation (KC stimulation with *Corynebacterium parvum* or inhibition with gadolinium chloride) is manifest in decreased or increased liver metastatic growth, respectively. Further work has shown that the predominant tumoricidal effector mechanism in vitro against the MCA 26 target is TNF dependent.[2,10]

Based on this work in the murine model, we have extended our investigations to humans and have demonstrated herein that human KC are cytotoxic against human colon adenocarcinoma in vitro. The KC from each patient were naturally cytotoxic against the targets. This observation would suggest that the resident KC in the patient are in a cytotoxic state. To determine if the isolation procedure introduced factors that activated the KC, all reagents and media were screened for the presence of endotoxin and were found to have no detectable levels. Alternatively, the location of the KC in the patient may explain this naturally cytotoxic state. The KC may be exposed in situ to various endogenous activators such as bacterial products in the portal venous blood as it drains the alimentary tract.

Despite the presence of the naturally cytotoxic state, the KC could be stimulated with exogenous IFN-γ and LPS. The capacity of the KC to undergo further stimulation may ultimately allow these effector cells to be used as a therapeutic modality. These specific agents and the activation sequence were chosen based on prior investigations with murine KC.[10] The IFN-γ acts as a priming signal that places the KC in a partially activated state. The LPS acts as a triggering signal that produces significant stimulation of cytotoxicity. It is possible that IFN-γ and LPS are not ideal signals to produce maximal human KC stimulation. Further studies will be necessary to identify the signals that can produce optimal activation.

An understanding of the KC cytotoxic mechanisms is required if these effector cells are ultimately to be used to treat metastatic growth. This study has demonstrated that human KC produce soluble TNF and this production is increased significantly by stimulating the KC. The importance of this production is uncertain because anti-TNF antibody, even at levels that totally quenched the biologic activity of soluble TNF, failed to inhibit KC lysis of the HT 29 targets. One interpretation of these observations is that the KC mediate cytotoxicity with a membrane-bound form of TNF.[4,11-14] In this case, direct KC-target cell contact is required to effect cytotoxicity, and substantially higher doses of anti-TNF antiserum might be required to inhibit the membrane-bound cytokine. Current studies in this laboratory are investigating the role of membrane-bound TNF in mediating cytotoxicity.

Another possibility is that the human KC do not mediate cytolysis against HT 29 with a TNF-dependent mechanism. Other work in this laboratory has demonstrated that significant quantities of interleukin-1 are produced by the activated KC. Potentially this cytokine or its membrane-bound form may mediate cytolysis against the HT 29 targets. To understand better the scope of human KC tumoricidal effector mechanisms, we are investigating KC cytotoxicity against a panel of human tumor cell lines that might be representative of tumors whose natural history predicts a predisposition for hepatic metastases.

Although it is important to identify the KC cytotoxic mechanisms, it is also necessary to understand the regulatory controls. Prior work in this laboratory has demonstrated that hepatocytes exert a profound inhibitory influence on murine KC tumor cytotoxic function, and this effect is reproduced with hepatocyte supernatant.[15] This regulatory influence is specific for hepatocytes because the effect cannot be reproduced with murine fibroblasts Another study has also described hepatocyte modulation of the cytotoxic function in the liver.[16] Isolated hepatocytes alone did not exert in vitro cytotoxicity yet they were shown to inhibit cytotoxicity when cocultured with a nonparenchymal cell suspension (containing KC and other hepatic cell populations). If the KC are ultimately used to treat liver metastases, it is important to understand these regulatory controls.

In summary, this study has shown that human KC are cytotoxic against human colon adenocarcinoma. This cytotoxic activity can be stimulated significantly and the KC secrete TNF. Lysis of the colon adenocarcinoma targets appears to proceed in a mechanism that is independent of soluble TNF.

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Correspondence

Aetiology of venous ulceration

Letter 1

Sir

In his leader on venous ulceration, Mr Burnand (*Br J Surg* 1990, **77**: 483–4) places great emphasis on the fibrin cuff hypothesis. Central to this hypothesis is the proposal that pericapillary fibrin (which is found in the dermis around venous ulcers) acts as a 'diffusion block to the passage of oxygen and other nutrients to the skin'

While not impossible, it seems most unlikely that pericapillary fibrin can reduce the diffusion of oxygen to such critical levels. The diffusion of oxygen through a fibrin gel is hindered by collision with the polymerized fibrin molecules and is restricted to the fluid filled spaces between them. Since the molecular radius of oxygen (0·1 to 0 2 nm) is small compared with the radii of the cylindrical chains of fibrin molecules (5 to 10 nm), the apparent diffusion coefficient of oxygen is reduced as a function of the volume of the gel occupied by the fibrin. The precise relation between the reduction of the diffusion coefficient and the volume concentration of the fibrin depends upon the arrangement of the fibrin chains If they were distributed randomly, the oxygen diffusion coefficient would decline exponentially with fibrin concentration[1]. Diffusion is impeded most effectively by uniformly spaced 'fibres', when the diffusion coefficient falls directly with the volume of fibrin per unit volume of gel[2].

Thus, if the fibrin polymers occupy 50 per cent of the volume of the pericapillary cuffs in the skin surrounding venous ulcers, the diffusion coefficient of a small molecule such as oxygen, is reduced to only half its value in free aqueous solution even if the fibrin polymers are evenly spaced.

It should be noted that the apparent diffusion coefficient of oxygen through cellular tissues such as muscle is approximately half its free diffusion coefficient in aqueous solution. This means that fibrin would have to occupy more than 50 per cent of the volume of the pericapillary cuff before it would begin to act as a significant barrier to the diffusion of oxygen. Such concentrations of fibrin would be remarkably high. The fibrin concentration in a clot of fresh plasma is related to the precoagulation levels of fibrinogen which are normally in the range of 0·4 to 0 5 per cent Thus to hinder diffusion significantly, the fibrin concentration in a pericapillary cuff would have to be concentrated over 100 × more than it is in a plasma clot. While it is probable that higher concentrations of fibrin may be present in pericapillary cuffs than in plasma coagulates, it is difficult to understand how such very high concentrations could be achieved or maintained *in vivo*.

Mr Burnand suggests a pericapillary diffusion barrier is necessary to account for the interesting observations of Hopkins *et al* [3] who from positron emission data concluded that blood P_{O_2} was lowered in areas of lipodermatosclerosis A more likely explanation is heterogeneity of microvascular flow in these regions. Tissue hypoxia can result from a failure of the distribution of microvascular flow to match local metabolism just as arterial hypoxaemia can result from non-uniformity of alveolar perfusion and alveolar ventilation. Only when heterogeneity of microvascular flow can be discounted need one consider barriers to oxygen diffusion.

At present it seems there is no evidence for the existence of a pericapillary diffusion barrier in tissues associated with venous ulceration and no evidence that the fibrin concentrations in pericapillary cuffs can be high enough to seriously impair the diffusion of oxygen. Until such evidence is forthcoming it is difficult to regard the fibrin cuff hypothesis seriously.

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Letter 2

Sir

We read with interest the leading article by Mr Burnand (*Br J Surg* 1990; 77·483–4) We are pleased to see the omission of any discussion regarding the perforating veins in venous ulceration, with emphasis on varicose veins and deep vein thrombosis as the more important factors Whilst objective assessment has so far failed to demonstrate the precise role of perforating veins in this disease, there can be no doubt that incompetent valves in the longitudinal deep or superficial veins may result in ulceration We are disappointed that Mr Burnand did not acknowledge primary valve failure in the absence of previous deep vein thrombosis as a significant clinical entity, as described by Kistner[1] From their own publications it seems that this forms a significant proportion of the patients presenting with ulceration in the UK.

We are distressed by the perpetuation of the unlikely suggestion that pericapillary fibrin cuffs are primary in the pathogenesis of venous ulcers. Mr Burnand presents some evidence to support his hypothesis, but does not discuss the conflicts which such a mechanism has with published data. The hypothesis that white blood cells are part of the processes seems to be dismissed too lightly. The reasons why the 'white cell supporters club' prefers a more complex explanation than the 'fibrin cuff buffs' are many, but fall into three main groups. The first is that such a mechanism as proposed by Browse and Burnand is unique in human pathology; although fibrin cuffs occur in all inflammatory processes as a consequence of increased capillary permeability, it is only in venous ulceration that it is proposed that these result in decreased oxygenation of the tissues. The second is that there is little evidence to support the assertion that skin damage in venous disease is attributable to hypoxia or ischaemia. The third is that the processes invoked by us from the literature on white cell metabolism and microcirculatory phenomena are commonplace in all inflammatory diseases and in critical ischaemia induced by insufficient arterial blood supply It can easily be demonstrated that an ulcer may be produced in normal skin within a few hours by the activation of such white cell mechanisms.

The role of the fibrin cuff in restricting the supply of oxygen to the tissues is central to the 'cuff buffs' case. There is no published evidence to prove that fibrin provides a barrier to oxygen diffusion. The literature cited by Mr Burnand probably refers to their own measurements, made on a fibrin sheet. No attempt seems to have been made to determine the composition of this material It is probable from the composition of other human connective tissues that the fibrin gel of the pericapillary cuff would comprise much water with a small amount of fibrin. Diffusion rates of small molecules, such as oxygen, through this material are expected to be very similar to water (Professor Charles Michel, personal communication), contrary to the suggestion of the fibrin-cuff hypothesis

The evidence which is advanced to support the assertion that tissue damage is due to hypoxia comes from transcutaneous oxygen measurements[2,3], no direct measurements having been published. In venous disease, different findings have been obtained depending on whether the transducer is heated to 43 or 37°C. At the higher temperatures, used by most authors, it has been found that patients with venous disease tend to have lower P_{tc,O_2} readings than normal subjects. There is a substantial overlap in P_{tc,O_2} between patients with normal limbs and those with liposclerotic skin, with some 'normal' subjects having lower readings than patients with liposclerotic skin. Measurements made with an electrode temperature of 37°C are paradoxical[5]. Under these circumstances, the oxygenation of the skin is greater in patients with venous disease than in normal subjects! The liposclerotic skin with the lowest oxygen tension is that of *atrophie blanche*, yet this condition may persist without ulceration for many months or years Clearly oxygenation is not the only factor important in determining the development of venous ulceration

In 1982 it was not an unreasonable suggestion to advance the argument that the prevention of gaseous exchange between capillaries and the surrounding tissues would lead to ulceration, since this was thought to be the mechanism of critical ischaemia. Subsequent advances have shown that this is clearly not the case, and that the damage caused to tissues during hypoperfusion or reperfusion is substantially due to white cell occlusion of capillaries, activation of white cells and aggregation of platelets Tissue destruction is caused by the release of superoxide radicals and proteolytic enzymes from neutrophils and monocytes, and to a much lesser extent from the prevention of oxygen exchange with the tissues This is a classical experiment to show that myocardial infarction in the dog can be prevented by rendering the animal neutropoenic before clamping a coronary vessel for 30 min[5]

In view of the difficulties of assessing oxygen delivery, we have measured the clearance of xenon from the skin during postischaemic hyperaemia as an estimation of the efficiency of the circulation in handling a molecule of similar size to oxygen Measurements were made in the supramalleolar region of patients with venous disease causing lipodermatosclerosis, and patients of similar age distribution without venous or arterial disease There are substantial overlap between the subjects and controls when comparing the half clearance time from the skin. These results demonstrated no significant abnormality of function of the microcirculation in venous disease in handling a molecule of the size of xenon We would expect a substantial perfusion deficit, if this alone were to cause the skin changes of lipodermatosclerosis and ulceration

One therapeutic possibility in the management of venous disease is the use of profibrinolytic agents to promote absorption of the fibrin cuff In a preliminary study Mr Burnand was able to demonstrate histological evidence that such an approach was effective, using the profibrinolytic anabolic steroid stanozolol[6] A subsequent study has been undertaken to establish whether stanozolol was useful in the management of venous ulceration, but showed that this did not influence healing after 75 patients had been studied for 28 months[7].

Mr Burnand states that we examined only the normal skin of patients with liposclerotic changes. This is not the case! The results published in the *British Medical Journal*[8] were taken from observations on liposclerotic skin, contrary to Mr Burnand's suggestion Patients were examined only in the supine position so that a persisting effect of venous hypertension could be observed without any uncertainty about the influence of a change in posture on the measurement technique. The data from such observations are open to many interpretations, but we believe that they did suggest the development of a microcirculatory deficit following a period of raised venous pressure. From the data presented above, it can be seen that we have been unable to show that this is of material importance in altering the perfusion of the skin using the technique xenon clearance

It is suggested by Mr Burnand that white cell trapping has not been shown in normal skin in control subjects This also is untrue Professor Michel and colleagues were able to show that white cell 'trapping' can be produced in normal legs by raising the venous pressure on sitting with the lower limbs dependent[9] In this study haematological measurements were made on blood taken from the long saphenous vein at the ankle. We have subsequently been able to produce white cell trapping in the upper limb, by simply applying a cuff to the arm and inflating it to 80 mmHg for a period of 15 min Blood taken from the hand and arm under these circumstances showed relative white cell depletion at the end of the period of raised venous pressure.

The presence of increased numbers of white cells in histological sections of liposclerotic skin is described in dermatology texts In order to quantify this we took biopsies of the skin of the supramalleolar region of patients undergoing varicose vein surgery in patients with and without liposclerotic changes The number of white blood cells visible per unit area in the upper 0 5 mm of the skin in each histological section was estimated by an observer who was unaware of the diagnosis There were between eight and 40 × as many white cells in liposclerotic skin than that from patients without skin changes

One might say that the proof of a new hypothesis (of pathogenesis) is in the treating! Is there any evidence from therapeutic measures that attempting to modify these effects has any influence on venous disease? The cytokine antagonist, pentoxifylline, has already been evaluated in this respect. Pentoxifylline antagonizes the effect of TNF_α and IL-1 on polymorphonuclear neutrophils, resulting in much lower likelihood of adhesion and activation[10] In a multi-centre study in which 80 patients were entered, pentoxifylline has been shown to result in significantly better healing rates of venous ulcers than placebo[11]. Prostaglandin E_1 inhibits the respiratory burst of neutrophils, preventing the release of superoxide radicals A preliminary study has suggested that this too is effective in healing venous ulcers[12] The magnitude of effect was much greater in both of these studies than that observed with the profibinolytic agent stanozolol

To those not directly involved in venous disease research it may seem that such intense discussions about pathogenesis are unnecessarily involved and unproductive Yet we have been applying the same treatment to legs for venous ulceration (bandages and dressings) since the time of Hippocrates, and unless there is a more complete understanding of the pathogenesis of this disease there will be no advance. Investment in appropriate research might well provide a reliable explanation for the problem, leading to better ways of healing ulcers and preventing their recurrence.

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A technique for varicose vein surgery

Sir

We were interested in Messrs Chester and Taylor's elegant technique for marking veins accurately (*Br J Surg* 1990; **77**. 560–1) However, in their description of stripping veins they imply that traditional vein strippers have the disadvantage of requiring a larger incision around the knee for its removal

We use a Myer's vein stripper, which has a (13 mm) head A catgut tie is used to fix the proximal end of the long saphenous vein to the stripper and one of the ends is left long enough to allow retrieval back through the groin incision following stripping. The vein is stripped in the usual way and a small incision made below the knee to allow removal of the distal end of the stripper

The vein is then removed through the incision and the stripper retrieved by withdrawing the catgut tie along the track left by the vein.

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Endoscopic sphincterotomy in hepatic hydatid disease open to the biliary tree

Sir

We read with interest the article by M. L. Vignote and colleagues (*Br J Surg* 1990, **77**, 39–1). We would agree, in general, about the value of endoscopic sphincterotomy (ES) for the complications of hydatid disease but found their article unclear to the indications for and timing of ES.

Recently we reviewed a 3-year experience of hepatic hydatid disease at the Departments of Gastrointestinal Surgery and Gastroenterology in the Turkey Advanced Specialization Hospital. During this period, 156 operative procedures were carried out and ten patients were treated by endoscopic drainage for pre- or postoperative complications. We wish to highlight some important differences in their management from the series reported by Vignote *et al*

Of the ten patients in our study two were successfully treated before operation by ES and nasobiliary drainage, one presenting with acute cholangitis and the other acute pancreatitis. In this group of patients Vignote *et al* recommended the use of ES alone. We would suggest, however, that nasobiliary drainage in addition to ES may avoid the biliary tree again becoming blocked by hydatid elements before elective surgery.

Postoperative complications consisted of eight patients with biliary fistulae present for 3 weeks to 7 years after operation. External fistulae following surgery for liver hydatid disease usually close spontaneously[1] and we would not, therefore, consider intervention within the first 3 weeks of surgery unless other indications are present The duration of external biliary drainage was not stated in the report by Vignote *et al.* and these fistulae may have closed spontaneously without ES.

Six of the eight patients with external biliary fistulae were treated with nasobiliary drainage alone and a further two, in whom papillary stenosis was present, had ES before nasobiliary drainage. All fistulae closed within 4 weeks of biliary tract drainage We would recommend leaving a nasobiliary catheter in this situation rather than carrying out ES alone, as recommended by Vignote and colleagues, thus allowing low pressure suction to be applied to ensure adequate biliary decompression as well as facilitating further cholangiography.

In conclusion we would recommend a selective policy of ES and/or nasobiliary drainage for the pre- or postoperative complications of liver hydatid disease depending on the findings at endoscopic cholangiography. Although Vignote and colleagues had no morbidity and mortality associated with ES this would undoubtedly alter in a larger series[2].

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Authors' reply

Sir

We acknowledge Drs Akoglu, Davidson and colleagues' comments on our paper[1]. Endoscopic sphyncterotomy (ES) for external biliary fistulae was indicated in our patients because the fistulous tract had not healed for a period ranging from 25 to 55 days (mean 31.4 days). These external biliary fistulae appeared within a few days after surgery for liver hydatid disease. The persistence of the fistulous tract can be attributed to an obstructed bile flow through the papilla and the consequent increased pressure within the biliary tract. This explains the need for ES. Most authors recommend prophylactic cholecystectomy during surgery for hepatic hydatid disease open to the biliary tree since it reduces the high incidence of infectious complications of ES under these circumstances[2]. Seven of our ten patients underwent cholecystectomy. The mean follow-up was 32 months (6–84 months) and no complications were observed during this time. Lastly, we agree with Dr Akoglu *et al.* on the role of nasobiliary drainage in the patient with acute cholangitis, if adequate drainage can not be obtained with ES or if he is critically ill[3] However, our two patients had a stable clinical status, and the biliary tract had been properly cleared of hydatid elements in both of them with ES.

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Endoscopic sphincterotomy for bile duct stones in patients with intact gallbladders

Sir

The paper from Hansell and colleagues (*Br J Surg* 1989, **76**: 856–8) is a useful addition to the accumulating body of information on the fate of the intact gallbladder following endoscopic management of common bile duct stones. However, we believe that the authors have been unduly pessimistic in the interpretation of their data.

In their study of a high risk elderly group of 121 patients (mean age 80 years) the overall procedural/biliary related mortality rate was only 6 6 per cent and 75 per cent remained asymptomatic for a median follow-up period of 24 months. Despite this, the authors were concerned that 18 per cent of their patients required cholecystectomy for recurrent symptoms No mention was made of the mortality rate in those patients requiring subsequent cholecystectomy but they expressed concern that with increasing duration of follow-up many more patients will develop biliary related complications and by inference that there will be related deaths.

However, our experience suggests that this fear is probably unfounded as it is more likely that these patients will die from associated medical conditions. We have followed up 72 patients with intact gallbladders for a median interval of 19 months after successful endoscopic clearance of their bile duct stones Fifteen patients (21 per cent) developed biliary related complications resulting in one death Ten of the 15 patients with biliary complications were managed surgically with no deaths. No fewer than 12 of the remaining 57 patients died of associated medical conditions

We do not believe that the results in this study support a more aggressive surgical policy towards the intact gallbladder. On the contrary, the evolving range of non-operative/minimally invasive procedures may reduce the need for cholecystectomy even further[1,2,3]

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Operative cholangiography in elective cholecystectomy

Sir

We read with interest the article by Pernthaler *et al.* (*Br J Surg* 1990, **77**. 399–400) on selective intraoperative cholangiography in elective cholecystectomy. While previously an operative cholangiogram was performed with every contentional cholecystecomy in our clinic, the introduction of the new technique of laparoscopic cholecystectomy has completely altered our operative management. We are presently reviewing the results of 100 patients who underwent laparoscopic cholecystectomy (97 per cent successfully) between October 1989 and April 1990 Since this is a new surgical procedure, patients with a history of jaundice, acute cholecystitis, pancreatitis, raised liver enzymes or a dilated common bile duct on ultrasound were excluded from this prospective trial All other patients with symptomatic gallstones were included. An intraoperative cholangiogram was not performed in any of these patients This policy is based on the findings of others[1,2] which show that raised preoperative biochemistry, a history of jaundice or pancreatitis, or a dilated common bile duct are reliable indicators of common bile duct stones. As endoscopic stone extraction is a safe and established procedure[3] performed by the general surgeons in our clinic, we did not exclude patients with small stones from our trial With a mean follow-up of 4 months, no patient has represented with retained common bile duct stones.

We have recently commenced the second phase of our prospective study with inclusion of all patients with symptomatic gall stones Duct visualization and stone extraction is being performed before operation where indicated Again no patient is undergoing intraoperative cholangiography and our policy is to perform endoscopic retrograde cholangiography (combined with papillotomy and stone extraction if necessary) should patients represent with postoperative biliary symptoms

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Use of fresh porcine bowel in surgical training

Sir

Courses in surgical technique have become popular[1–3]. Some objection has been raised to the use of fresh bowel from recently slaughtered animals for teaching of bowel anastomosis techniques[3] We have used fresh porcine bowel for this purpose with good results.

Small bowel, with mesentery intact, from newly slaughtered pigs is obtained free of charge from a local abattoir. The bowel is taken directly to the hospital's post-mortem room which is used 'after hours' as a surgical workshop The bowel is immediately rinsed of its content and appropriate segments excised for use Surgical gloves and a protective plastic apron are used. Working in groups of two, the mesentery is dissected, ligated and transected to simulate a bowel resection. Various techniques of bowel anastomoses are taught, e g. one layer, two layer, interrupted sutures, continuous suture, end-to-end and side-to-side After the session the instruments and post-mortem room are cleaned by the trainees and the instruments packed and sent for sterilization. The same instruments are used again at subsequent sessions

The rinsed bowel is odourless and pleasant to work with. The bowel is similar to human bowel in calibre, macroscopic structure, handling properties and tensile strength. Experience gained from anastomosing pig bowel could thus easily be transferred and used in the clinical situation. The bowel remained fresh and maintained its physical properties as long as 4 h after slaughter without any preservation or cooling. This was adequate for the 30 min transport time and 2 h workshop session The rinsed bowel, immersed in normal saline and refrigerated, could be kept a few hours longer

After 6 months (12 sessions) of using fresh bowel, we have experienced no mishaps in the form of infection of the trainees or instructor. All eight trainees have been satisfied with the condition of the porcine bowel and their ability to learn the techniques on it.

The use of fresh unprocessed tissue from newly killed animals for teaching purposes has been criticized by Stotter *et al.*[3] in that it is 'messy, smelly, [and] has potential for infection'. They have suggested using gamma irradiated, freeze dried animal intestine instead. We have encountered none of these problems. The advantages of using fresh porcine intestine are that it is free and readily available (in Denmark) and it closely resembles human bowel. The expense and technology required for special preparation of the tissue is avoided

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T tube intubation in the management of oesophagopleural fistulae

Sir

We read with interest the article written by Naylor *et al* (*Br J Surg* 1990, **77**. 40–2). We agree with the authors that this method, albeit unpopular, 'offers a potential alternative to major surgical intervention' Further, it may eventually serve as an organ preserving procedure

We recently treated a 2-year-old child with an extensive, deep, corrosive, caustic oesophageal burn, involving the mid- and lower oesophagus, complicated by perforation with severe mediastinitis and a right pneumothorax At urgent surgery all the thoracic oesophagus was damaged and friable Suture of the perforation was not feasible. Complete resection with cervical oesophagostomy and subsequent later interposition had been suggested by the attending general surgeon present at the operation Instead, intubation by a long T tube through the perforation was done and all the oesophagus was wrapped by an omental flap pulled up through the hiatus The mediastinum and the right pleural cavity were debrided, irrigated and drained A Stamm gastrostomy was performed The T tube remained in place for 1 month and no leak appeared, however, a 3 cm long stricture developed in the mid-oesophagus. Repeated dilatations failed to resolve this complication Re-thoracotomy was performed 8 months later, with resection of the stricture and an end-to-end anastomosis, achieving a good functional result although later fundoplication and pyloroplasty were necessary for reflux and delayed gastric emptying.

Now, 14 months after the burn, the child is capable of eating solid food. He is still under observation and undergoes sporadic oesophageal dilation to prevent re-stricture Undoubtedly this result is better than oesophagectomy with interposition.

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A randomized trial of oral 5-FU *versus* placebo in colorectal cancer: results of 10 years observation time

Sir

Adjuvant chemotherapy of colorectal cancer has been tested for more than 15 years, yet no single study convincingly supports treatment as better than no treatment. There is one major exception to this statement and that concerns regional portal infusion, which reduces mortality mainly in stage Dukes' B[1]. These results are partly supported by one Swiss and one Australian–New Zealand study[2,3].

In a meta-analysis of adjuvant therapy there were data supporting a minor statistical borderline benefit in survival of chemotherapy – both concerning 5-fluorouracil (5-FU) alone and the combination of 5-FU with nitrosourea[4].

From 1976 to 1978 a controlled randomized trial of peroral 5-FU *versus* placebo was conducted on patients with Dukes' B and C colorectal cancer. It was stated that there was a borderline significant effect in Dukes' B[5]. Peroral 5-FU could thus have an effect in patients with a minimal tumour burden, which eventually could be recognized after a longer observation time. This motivated a re-evaluation of the trial after 10 years

The material is described in the previous presentation. The survival of patients 10 years after randomization was taken from the official Swedish population statistics There is no missing information for any patient at 120 months.

Survival times were analysed by the life-table (actuarial) method. Differences between groups were evaluated by the Lee-Desu statistic and by χ^2 tests. The Lee-Desu statistic is a generalized Wilcoxon test. All *P* values refer to two-tailed tests as a negative influence of instituted therapy could be possible.

After a minimum of 10 years after the last randomized patient was entered into the trial the survival was 45 per cent in both placebo and treated group There was a statistically significant difference in Dukes' B rectal cancer with 61 per cent, 10 years survival, in the treated group *versus* 40 per cent in the control group. If this finding is a chance of a real phenomenon, it has to be explored in further studies. Co-ordinators for other previous studies on adjuvant treatment of colorectal cancer are urged to do a similar evaluation after 10 years.

Table 1 *Survival at 10 years*

	Placebo *n*	5-fluorouracil *n*
Dukes' B		
Colon	68 (62)	69 (59)
Rectum	30 (40)*	31 (61)*
Total	98 (55)	100 (60)
Dukes' C		
Colon	50 (46)	53 (40)
Rectum	25 (28)	31 (26)
Total	75 (40)	84 (35)
Limited clearance	32 (25)	32 (25)
Total material	205 (45)	216 (45)

Values in parentheses are percentages. * $P=0{\cdot}04$

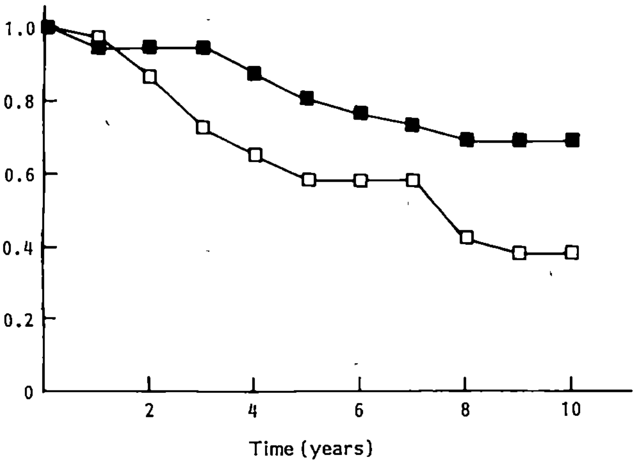

Figure 1 *Survival Dukes' B rectum* ($P=0{\cdot}04$) □, *Placebo Dukes' B rectum*, ■, *treatment Dukes' B rectum*

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Bile leakage after removal of T tubes from the common bile duct

Sir

We have read with interest the papers by Ryttov *et al* (*Br J Surg* 1989, **76**: 1319) and by Horgan *et al.* (*Br J Surg* 1989, **76**: 1296–7) about the drainage of the bile duct with a T tube.

The majority of the Spanish surgeons experienced in biliary surgery have treated patients with bile spillage after simple cholecystectomy and after the removal of a T tube We believe that there is a relationship between the irritant nature of the tube and bile spillage[1]. However, the clinical problem after bile leakage is variable The bile leak rate observed in patients who underwent cholecystectomy with bile duct exploration is 0·66 to 9 per cent, but the re-operative rate for these patients is low[2], a decision based on clinical rather than radiological findings.

We believe that the complications associated with the insertion of a T tube do not justify its use after a simple exploration of the bile duct[3].

Extraction of bile duct stones is followed by 0·5 to 5 per cent of residual stones[4] In more than 95 per cent of patients T tube bile duct drainage is unnecessary. To date, and because of the routine use of the endoscopic papillotomy and nasobiliary drainage it is possible to practice primary closure of the bile duct.

Finally, we believe that there are only three circumstances where the use of a T tube is mandatory: cholangitis, papillary blockage and coexistence of pancreatitis. The coexistence of a previous gastrectomy Billroth II is not sufficient to exclude primary closure of the biliary duct

In our experience, a meticulous bile duct exploration with peroperative cholangiography and manometry is sufficient to enable primary closure of the bile duct to be performed safely

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Book reviews

Patient Controlled Analgesia

F M Ferrante, G W Ostheimer and B. G. Vocino. 165 × 241 mm Pp 231 Illustrated. 1990 Oxford Blackwell Scientific Publications £32.50 hardback

It has long been recognized that patients vary tremendously in their perception of pain and their requirements for analgesia It has also been shown in a number of studies that the traditional approach of prescribing opiates *pro re nata* provides poor pain relief for many patients because in practice patients do not receive drugs on demand but on the regular drug round Much time and effort has gone into the research for better analgesic drugs but very much more effective pain relief can be achieved using the drugs we already have by more effective routes of administration and delivery systems. Hence the growing popularity of patient controlled analgesia in which patients can administer doses of analgesic to themselves at the press of a button within limits prescribed by the physician.

This book, edited by anaesthetists from Harvard Medical School, but with contributions from many centres in the USA is therefore very timely. The theory and practice of patient controlled analgesia, its application to different types of pain, the economics and logistics of introducing patient controlled analgesia are discussed in 23 chapters with a host of up-to-date references Despite there being more authors than chapters there is little repetition, although three figures do appear twice in different places For surgeons the message is that patients like it and it is as safe as any other method of analgesia. For UK hospitals contemplating a future in which the Government requires us to be more competitive while facing a nursing shortage it is interesting to learn that in the USA it has been found economically viable and required less nursing time, freeing them for other tasks Surgeons not already using patient controlled analgesia in their practices will find in this well written book all they need to know for introducing it

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Atlas of Surgical Management of Anorectal Malformations

A Peña 180 × 260 mm Pp 104. Illustrated. 1990 New York Springer-Verlag £60 00 hardback

Anorectal malformations are some of the most challenging problems presenting to paediatric and colorectal surgeons Following unsatisfactory results obtained with pull through operations, where definition of pelvic floor anatomy was often difficult, Professor Peña introduced the posterior sagittal approach In this book he presents his experience in over 400 patients. There is a wealth of practical technical operative advice and the illustrations are superb Each procedure is described step by step starting with the more straightforward anomalies and leading on to the complex At the end of the book is a section on secondary operations, using the posterior sagittal approach in cases of a previous unsuccessful pull through procedure

My criticisms are relatively minor The use of the royal 'we' is rather irritating, and the final chapter on results was disappointing The short term morbidity and mortality was described sketchily, and postoperative functional assessment only briefly outlined. Most important of all, what are these children like when they are teenagers since this is the time of late functional failure for the conventional operations? Nonetheless this operative surgical handbook will be an invaluable guide to specialist paediatric and colorectal surgeons grappling with these often formidable congenital abnormalities

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Reductive Mammaplasty

R M. Goldwyn 190 × 260 mm Pp 587 Illustrated 1990 Boston Little Brown–Churchill Livingstone £130 00 hardback

The multiplicity of operative techniques of reduction mammaplasty is testament to the fact that no single technique can produce a 'perfect' result in all patients. In his book Dr Goldwyn has compiled the experience of many authors to provide the reader with an authoritative overview of the currently available techniques

The early chapters address the historical perspective of reduction mammaplasty, the vascular anatomy of the breast and the pathophysiology of breast enlargement The chapter on the mammographic appearances of the breast after reduction mammaplasty is recommended to radiologists as well as surgeons but I do not think the necessity of preoperative mammography in patients over the age of 30 years has been sufficiently stressed Dr Goldwyn discusses the problem of the unsuspected breast cancer in more detail in a later chapter. Dr Cline's contribution on the psychological aspects of breast reduction surgery is well written and is recommended to all those currently involved in this field or wishing to develop an interest. Saul Hoffman's chapter on the medico-legal aspects was clearly written with the USA practice in mind but I consider it to be of equal value to surgeons in the UK, and not only those involved in plastic or reconstructive surgery

The bulk of this text is devoted to descriptions of many of the currently used techniques for reduction mammaplasty by undoubtedly experienced and authoritative clinicians The operative techniques and specifically the preoperative assessment and marking are generally well described, with particularly clear contributions from Pitanguy, Bricout and Mouly, Goldwyn and Courtiss, Peixoto, and Gradinger. Dr Goldwyn concludes with a warning of the complications and unfavourable results obtained with reduction mammaplasty

This book is clearly aimed at experienced plastic surgeons and those in training and as such is well executed It is not a 'workshop' manual to allow an inexperienced surgeon to dabble in cosmetic breast surgery It is a worthwhile addition to the library of any plastic surgery unit engaged in this work

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Breast Cancer

B. J Kennedy 180 × 260 mm Pp. 240 Illustrated 1989 New York· Alan R Liss Incorporated £75 00 hardback.

This is a well presented book in the form of a multi-author monograph in the series *Current Clinical Oncology* Presentation is clear, concise and well illustrated with a combination of line drawings and clinical photographs The authors have synthesized the large body of published information on the disorder into a readable text which encompasses the most up-to-date information. All aspects of the diagnosis and management of the condition have been covered from discussions of the aetiology to the biological features of the disease with reference to laboratory data and genetics

The multi-authorship has allowed the inclusion of a broad spectrum of specialist opinion and includes discussion on malignant breast disease, breast reconstruction and the role of adjuvant treatments Whilst the presentation and approach has a North American slant, the book is highly recommended to undergraduate and postgraduate alike

Any general surgeon practising breast surgery should include this volume on his book-shelf

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Thoracic Surgical Techniques

F Wells, B B Milstein. 200 × 295 mm Pp 280 Illustrated 1990 London Baillière Tindall, £80 00 hardback

This is an excellent book. All aspects of non-cardiac thoracic surgery are covered, including diagnostic procedures. It should be required reading for thoracic surgeons in training who intend to pursue a career in pulmonary and oesophageal surgery It will also be of great value to general surgeons, who do not have easy access to a thoracic unit and who need to enter the chest on occasions

Aspects covered in the text include diagnostic procedures, such as rigid and flexible bronchoscopy, mediastinoscopy and thoracoscopy, and all aspects of tracheal, pulmonary, oesophageal, mediastinal and chest wall surgery Each section is preceded by the essential anatomy and the basic indications for the procedure The reader is taken step-by-step through each operation, assisted by numerous, very clear, and well presented line drawings There are many tips, which have only been acquired by long experience, and which make the dissection easier and safer so avoiding many of the common pit-falls. It is refreshing to see that basic suture techniques are described in detail for both pulmonary and oesophageal resection With the advent of modern stapling instruments, it is still essential to be adept in the standard suturing techniques in case the stapling instruments are not available or rarely if there is an instrument failure.

The section on oesophageal surgery gives a rational approach to the management of hiatus hernia and stresses the importance of preoperative assessment, including oesophageal manometry and pH studies Reconstruction of the oesophagus for malignant disease using stomach, jejunum and colon are particularly well described and there is one section on the technique for creating a stapled oesophagogastric anastomosis

I think this book should be highly recommended

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Surgical Audit

A. Pollock, M. Evans 170 × 240 mm Pp 160. Not illustrated 1989 London Butterworths £19 50 hardback

In a foreword to this slim volume Hiram Polk states, 'There is nothing so fashionable as an idea whose time has come'. These two experienced authors have made a timely and worthwhile contribution to the literature on surgical audit with this book Despite its small size, indeed this is one of its attractions, a wide view of surgical audit is presented Any aspect of surgical clinical practice can be subjected to scrutiny and the various components are analysed individually The jargon of contemporary data collection and analysis is explained in sufficient detail to dispel misconceptions and correct ignorance. The major sections of the book comprise history, components of audit, audit of structure and process of outcome of patient satisfaction of ethics, of publications and the presentation of audit The review of audit of 'structure and process' illustrates the power of economic forces in determining provision of surgical care and experience from both sides of the Atlantic is described The failure of some overly ambitious projects, e g. the American Professional Standards Review Organisation should send a shiver of uncertainty through those responsible for instituting resource management and audit in the UK

Whilst emphasizing the positive aspects of accurately collected clinically led audit, the insidious potential of a potentially unfavourable outcome to influence clinical decision making, if every clinical decision is subject to critical review, is well made The crucial role of a measure of risk is rightly emphasized. The burden of data collection and analysis is not considered in great detail

This is a very readable overview of the problems which surgical audit will present in the next decade and it provides a broader perspective than most clinicians have of the scope and ramifications of audit It should be a useful link between clinicians and administrators and represents excellent value for money.

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Spinal Surgery: Science and Practice

R A Dickson. 220 × 280 mm. Pp. 548 Illustrated 1990. London Butterworths £140 00 hardback

This is a multi-author textbook on a topic which is becoming increasingly important. It has been aimed at the spinal surgeon in training (either orthopaedics or neurosurgical spinal surgeon), those sitting the specialist orthopaedic fellowship and those training in orthopaedics-in-general, it is concerned but less with 'what to do' than with 'what should be done, when and why'

The scope of the book is all encompassing from basic anatomy and physiology through the more common cervical spondylosis, lumbar disc disease and on to the less common metabolic and inherited disorders of the spine The first eight chapters cover surgical approaches, anatomical variations, physiology and pathophysiology, spinal pain, biomechanics and radiology and should be read by anyone contemplating any form of spinal surgery. There is an excellent chapter on lumbar disc disorders immediately followed by a smaller chapter on lumbar disc prolapse in adolescence which quite rightly is treated as a separate entity The remaining section on degenerative disorders has chapters on thoracic disc disorders, cervical disc and degenerative disease, inflammatory arthritis and the medical management and rehabilitation of spinal pain, within this there is a chapter on spinal microsurgery indicating a neurosurgical approach to these matters

There is an excellent section on spinal trauma covering the biomechanics and the general principles and this is continued into the chapters on cervical injuries, thoracolumbar injuries and neurological assessment, anyone dealing with spinal cord injuries should certainly read this section

My quibbles with the book are small ones in that some of the illustrations are poor especially in the chapter on spinal microsurgery and that in the chapter on radiological approaches to mechanical back pain the illustrations in *Figure 7 2c* and *d* have been reversed and there is an absence of labels in *Figure 7 14*; the chapter on thoracic disc disorders is rather thin and many classic references are not alluded to

These minor quibbles should not detract from the overall excellence of the book and I have absolutely no hesitation in recommending it as an essential text for anyone either in orthopaedic or neurosurgery contemplating spinal surgery as an interest

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Clinical Gastroenterology International Practice and Research July 1989: Colorectal Cancer

N Mortensen 230 × 155 mm Pp 737 Illustrated 1989 London Baillière Tindall £22 50 hardback

In the forward the Editor suggests that colorectal surgery has now come of age, this comment is particularly relevant with the increasing pressure for colorectal surgery to be recognized as a specialty in its own right This book will be read not only by acknowledged coloproctologists but it should also be of great interest to those beginning in the specialty The range of subjects discussed reflects the progress that is being made in coloproctology The authors of the individual chapters have been chosen for their known expertise in the subjects discussed and they provide good reviews of the current situation My only criticism would be that the chapters are arranged in a somewhat illogical order and I felt that the role, or non-role, of chemotherapy warranted a shorter chapter

I would encourage anybody interested in any of these subjects to use this book as a starting point for obtaining up-to-date 'state of the art' knowledge while the references make a good starting point for extending the reader's knowledge in the field of interest.

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Notices and announcements

20–21 September 1990
IV Annual Meeting of the European Society for Vascular Surgery
Rome, Italy
Information: Paolo Fiorani, Department of Vascular Surgery, University of Rome, School of Medicine, Policlinico Umberto 1, 00161 Rome, Italy

20–22 September 1990
Association of Surgeons in Training, 14th Annual Conference and AGM
Birmingham, UK
Information: Mr John Taylor, c/o Postgraduate Medical Centre, Queen Elizabeth Hospital, Edgbaston, Birmingham B15 2TQ, UK

23–28 September 1990
Comprehensive Review and Update of What's New In Vascular Surgery
Santa Monica, California, USA
Information: Dr W. S Moore, Professor of Surgery, Section of Vascular Surgery, UCLA School of Medicine, PO Box 24901, Los Angeles, California 90024-0901, USA

25–28 September 1990
1st International Conference on Ultrasound Angiography
London, UK
Information: Mr K. N. Humphries, 10 Swale Drive, Chandlers Ford, Hampshire SO5 3QY, UK

26–28 September 1990
Annual Scientific Meeting
University of Manchester
Information: Ann Muir, Association of Anaesthetists, 9 Bedford Square, London WC1B 3RA, UK

1–4 October 1990
Eurochirurgie: 92e Congres Francais de Chirurgie
Paris, France
Information. Secretariat Administratif, CONVERGENCES-AFC 90, 120 avenue Gambetta, 75020 Paris, France

3–6 October 1990
Principles of Colon and Rectal Surgery
Minneapolis, USA
Information. Continuing Medical Education, University of Minnesota Medical School, Box 202 UMHC, 420 Delaware Street Southeast, Minneapolis, Minnesota 55455, USA

5 October 1990
The role of the plain abdominal radiograph in the acute abdomen
Canterbury
Information: Postgraduate Administrator, Kent Postgraduate Medical Centre, Kent & Canterbury Hospital, Canterbury, Kent CT1 3NG

7–12 October 1990
Annual Clinical Congress of the American College of Surgeons
San Francisco, USA
Information: Ms Carol Williams, American College of Surgeons, 55 East Erie Street, Chicago, Illinois 60611-2797, USA

8–10 October 1990
Eleventh International Symposium on Information Technology in Anesthesia, Intensive Care and Cardiopulmonary Medicine
Rotterdam, The Netherlands
Information: Omar Prakash, Thorax Anesthesia, Thorax Centre, Erasmus University, 3000 DR Rotterdam, The Netherlands

18 October 1990
Cracking Gallbladders and Bile Duct Problems
London, UK
Information Charlotte McLeish, The British Institute of Radiology, 36 Portland Place, London W1N 4AT, UK

23–31 October 1990
Clinical Anaesthesia in the 1990s
Bristol, UK
Information: Louise Deakin, Courses Dept, The British Council, 65 Davies Street, London W1Y 2AA, UK

28 October–1 November 1990
42nd Postgraduate Assembly
Honolulu, Hawaii
Information: Ann Singer, Meetings Manager, The Endocrine Society, 9650 Rockville Pike, Bethesda, MD 20814, USA

29 October–3 November 1990
Fourth U.S. Phlebology Workshop in Paris
Paris, France
Information: Walter de Groot, 801 Broadway, Seattle, WA 98122, USA

2 November 1990
The Management of Complications Following Vascular Surgery
Newcastle-upon-Tyne, UK
Information. Mr J. Chamberlain, Ward 7 Office, Freeman Hospital, Freeman Road, High Heaton, Newcastle-upon-Tyne NE7 7DN, UK

3–7 November 1990
State of the Art in Digestive Surgery
Delhi, India
Information: Convention Centre, Hotel Taj Palace Intercontinental, Sardar Patel Marj, New Delhi 110021, India

5–9 November 1990
Annual Course in Hepatobiliary and Pancreatic Surgery
London, UK
Information: Wolfson Conference Centre, Hammersmith Hospital, Du Cane Road, London W12 0NN, UK

13–16 November 1990
2nd International Interdisciplinary Symposium
Vienna, Austria
Information Peritoneum and Peritoneal Access (PAX), F Schulz, c/o Vienna Academy of Postgraduate Medical Education and Research, Alser Strasse 4, A-1090 Vienna, Austria

15–17 November 1990
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11–13 December 1990
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Hong Kong
Information: Joseph W C Leung, Senior Lecturer in Medicine, Prince of Wales Hospital, Shatin, Hong Kong

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Hong Kong Surgical Forum
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Information: Forum Secretary, Department of Surgery, University of Hong Kong, Queen Mary Hospital, Hong Kong

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Meribel, France
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4th International Symposium on Cardiovascular Pharmacotherapy
Geneva, Switzerland
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4–5 May 1991
5th International Meeting of the Australian and New Zealand Society of Phlebology
Sydney, Australia
Information: Dr G Mark Malouf, Secretary, ANZ Society of Phlebology, PO Box 2166, North Paramatta 2151, Sydney, Australia

SURGERY

CONTENTS, AUGUST 1990
Volume 108 Number 2

Official Publication
SOCIETY OF UNIVERSITY SURGEONS, CENTRAL SURGICAL ASSOCIATION,
and **AMERICAN ASSOCIATION OF ENDOCRINE SURGEONS**

SOCIETY OF UNIVERSITY SURGEONS

Page 125 **Presidential address: Swimming with sharks—without the family being eaten alive**
Ernest E. Moore, MD,
Denver, Colo.

139 **Tamoxifen potentiates in vivo antitumor activity of interleukin-2**
Benjamin Kim, MD, Patricia Warnaka, BS, *and* Catherine Konrad, BS,
Salt Lake City, Utah, and Cleveland, Ohio

146 **Preneoplastic lesions induced by *myc* and *src* oncogenes in reconstituted mouse bladder**
Hans E. Wagner, MD, Glenn Steele, Jr., MD, PhD, *and* Ian C. Summerhayes, PhD,
Boston, Mass.

154 **Immunoprotective effect of a calcium channel blocker on macrophage antigen presentation function, major histocompatability class II antigen expression, and interleukin-1 synthesis after hemorrhage**
Wolfgang Ertel, MD, Daniel R. Meldrum, BS, Mary H. Morrison, MS, Alfred Ayala, PhD, *and* Irshad H. Chaudry, PhD, *East Lansing, Mich.*

161 **The effect of insulin-like growth factor I on postburn hypermetabolism**
Louis L. Strock, MD, Harbans Singh, PhD, Ahmed Abdullah, MD, James A. Miller, PhD, *and* David N. Herndon, MD,
Galveston, Texas, and Thousand Oaks, Calif.

165 **Insulin-like growth factor I receptors in the arteries of the rabbit: Autoradiographic mapping and receptor characterization**
Anton N. Sidawy, MD, Basel Termanini, MD, Ron V. Nardi, PhD, John W. Harmon, MD, *and* Louis Y. Korman, MD,
Washington, D.C., and Research Triangle, N.C.

172 **Effect of blood transfusions on immune function. Part VI. Effect on immunologic response to tumor**
J. Paul Waymack, MD, ScD, Gabriel Fernandes, PhD, Roger W. Yurt, MD, Jaya T. Venkatraman, PhD, David G. Burleson, PhD, Rey F. Guzman, BS, Arthur D. Mason, Jr., MD, *and* Basil A. Pruitt, Jr., MD.,
San Antonio, Texas, and New York, N.Y.

179 **Reversal of diabetic somatic neuropathy by whole-pancreas transplantation**
Marshall J. Orloff, MD, Glenn Greenleaf, BS, *and* Barbara Girard, BS,
San Diego, Calif.

191 **Trophic stimulation of the ductal/islet cell axis: A new approach to the treatment of diabetes**
Lawrence Rosenberg, MD, PhD, FRCSC, David Clas, MD, *and* William P. Duguid, MB, FRCPath,
Montreal, Quebec, Canada

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198 **Aerosolized cyclosporine as single-agent immunotherapy in canine lung allografts**
Robert D. Dowling, MD, Marco Zenati, MD, Gilbert J Burckart, PharmD, Samuel A. Yousem, MD, Michelle Schaper, PhD, Richard L. Simmons, MD, Robert L. Hardesty, MD, *and* Bartley P. Griffith, MD,
Pittsburgh, Pa.

206 **Inhibition of CD18-dependent neutrophil adherence reduces organ injury after hemorrhagic shock in primates**
William J Mileski, MD, Robert K. Winn, PhD, Nicholas B. Vedder, MD, Timothy H. Pohlman, MD, John M Harlan, MD, *and* Charles L. Rice, MD,
Seattle, Wash.

213 **Effects of glucocorticoids on lung glutamine and alanine metabolism**
Wiley W. Souba, MD, ScD, Donald A. Plumley, MD, Rabih M. Salloum, MD, *and* Edward M. Copeland III, MD,
Gainesville, Fla.

220 **Inhibition of parietal cell H+ secretion by transforming growth factor alpha: A possible autocrine regulatory mechanism**
Jonathan J. Lewis, MD, James R. Goldenring, MD, PhD, Irvin M. Modlin, MD, PhD, *and* Robert J. Coffey, MD,
New Haven, Conn., and Nashville, Tenn.

228 **Alterations in adipocyte adenylate cyclase activity in morbidly obese and formerly morbidly obese humans**
Louis F. Martin, MD, FACS, Carol M. Klim, MD, Susan J. Vannucci, PhD, Lori B. Dixon, BS, J. Richard Landis, PhD, *and* Kathryn F. LaNoue, PhD,
Hershey, Pa.

236 **Test performance of a local examination at a nonlocal site for evaluation of surgical clerks**
Gary Dunnington, MD, FACS, Don Witzke, PhD, James Hassett, MD, FACS, Liz Reisner, RN, John Fulginiti, MS, *and* Robert Rubeck, PhD,
Tucson, Ariz., and Buffalo, N.Y.

240 **Food without fiber promotes bacterial translocation from the gut**
Georg Spaeth, MD, Rodney D. Berg, PhD, Robert D. Specian, PhD, *and* Edwin A. Deitch, MD,
Shreveport, La.

248 **Effect of total jejunoileal denervation on fat-stimulated release of peptide YY and cholecystokinin**
B. Mark Evers, MD, Courtney M. Townsend, Jr., MD, Tatsuo Uchida, MS, George H. Greeley, Jr., PhD, Erick Allen, BA, *and* James C. Thompson, MD,
Galveston, Texas

254 **Both cyclooxygenase-dependent and cyclooxygenase-independent pathways mediate the neuroendocrine response in humans**
Hamish R. Michie, FRCS, Joseph A. Majzoub, MD, Sarah T. O'Dwyer, FRCS, Arthur Revhaug, MD, *and* Douglas W. Wilmore, MD, FACS,
Boston, Mass

262 **Reversible lung neutrophil accumulation can cause lung injury by elastase-mediated mechanisms**
Benjamin O. Anderson, MD, James M. Brown, MD, Denis D. Bensard, MD, Michael A. Grosso, MD, Anirban Banerjee, PhD, Anita Patt, MD, Glenn J. R. Whitman, MD, *and* Alden H. Harken, MD,
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This is a partial listing of August 1990 SURGERY contents

Br. J. Surg. 1990, Vol. 77, October, 1081–1082

Infection and the burn patient

Can ... the leopard change his spots?[1]

Burn patient survival has significantly increased during the past four decades as hypovolaemic shock, acute renal failure, invasive bacterial burn wound infection, Curling's ulcer, and metabolic wasting have been controlled by timely adequate resuscitation, topical chemotherapy, gastric acid control, and effective nutritional support. Even though infection of the burn wound is rare (only 8 per cent of infections in 1989), infection remains the major predator and most common cause of death in burn patients in whom the respiratory tract has now become the most frequent portal of infection[2]. The success of current burn wound care is further indexed by the change in the predominant form of pneumonia, haematogenous pneumonia that commonly arose from an infected burn wound, having been supplanted by bronchopneumonia. Pneumonia and bronchitis comprised 53 per cent of all infections in burn patients treated at the US Army Institute of Surgical Research during 1989. The importance of pneumonia as a co-morbid factor in critically ill patients is documented by its recognition as a cause of death in 50 per cent of fatal burns treated during the period 1983–1987[3].

The presence of *Pseudomonas* infections in burn patients in the late 1950s and early 1960s, considered by many to be a burn specific aberration, was validated by subsequent experience to have been an epidemiological premonition of infections in other critically ill patients. Since the 1960s the predominant infection-causing organisms in burn patients have continuously changed as evidenced by sequential mini-epidemics of infections caused by *Providencia stuartii*, *Enterobacter cloacae*, a recrudescent *Pseudomonas* species, and *Staphylococcus aureus* (the most frequently recovered pathogen in the past 6 years)[4]. During the past 13 years recovery of *Pseudomonas aeruginosa* from the blood and burn wounds has strikingly decreased, while recovery of staphylococci, Candida sp. and true fungi from those sources has increased[5]. The incidence of candidaemia has increased more than tenfold and filamentous fungi have become the most common cause of invasive burn wound infections, i.e. 18 of the 25 cases documented histologically during the period 1983–1987.

The increase in survival time of those burn patients who die, 17 days in 1970–1971 *versus* 24 days in 1986–1987, coincides with improvements in early post-injury care and a later onset of the currently common infections. The prevalence of pulmonary infections attests to both the success of initial ventilatory support in patients with inhalation injury and the microbial ecological hazard of prolonged airway intubation that permits conversion of the airway flora to that of the burn wound. The effectiveness of current burn care techniques is limited by both the extent of burn and the duration of treatment, as evidenced by the average time of diagnosis of candidal burn wound colonization (the 31st postburn day), and the average time of diagnosis of candidal infections of the urinary tract and other sites (even later in the second postburn month) The late occurrence of these non-bacterial opportunistic infections is consistent with their occupancy of the ecological niche that exists in extensively burned patients who have received one or more courses of broad spectrum antibiotics as treatment for earlier occurring bacterial infections and whose wounds remain open.

The ever changing character of this predator's spots answers Mr Kipling's question[1] in the affirmative and reinforces the importance of institutional infection control programs, including scheduled surveillance cultures of the wound, sputum, urine and stool, antibiotic sensitivity testing of index organisms, and the use of burn wound biopsies to assess the microbial status of the wound and guide both local and systemic therapy[6]. Studies demonstrating that the effects of infections are organism specific suggest that the recent changes in the epidemiology of infection in burn patients have contributed to the improvement in survival and survival time. Gram-positive bacteraemia or candidaemia exert no demonstrable effect on burn patient survival, while the previously prevalent Gram-negative bacteraemia significantly increased the mortality of burn patients above that predicted on the

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basis of age and burn size[7]. Cohort nursing can be used to interrupt the perpetuation of recrudescent nosocomial epidemics of those mortality enhancing organisms[8].

The persistence of injury induced immunosuppression until the burn wound is completely closed provides impetus for the development of techniques and technologies that will permit early permanent closure of even the largest burn and limit the time during which those patients are at risk to infection. The alterations in the microbial ecology of the severely burned patient induced by such improvements in care and the effects of antimicrobial agents directed against newly emerging pathogens may only induce further change in the leopard's spots. Infection as the predominant cause of morbidity and mortality in burn patients will persist and frustratingly qualify the success of new treatment techniques until effective regimens of immunological support are developed for those patients in whom the extent of burn, associated injuries or supervening complications delay wound closure.

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The opinions or assertions contained herein are the private views of the author and are not to be construed as official or as reflecting the views of the Department of the Army or the Department of Defense of the USA.

Leading articles

Br. J. Surg. 1990, Vol. 77, October, 1083–1084

Thrombolytic therapy in peripheral vascular disease

For more than 25 years it has been possible to perform thrombolytic therapy of peripheral arterial occlusions using streptokinase or urokinase. Until 10 years ago these were almost invariably administered systemically, i.e. intravenously. Systemic thrombolytic therapy has a good chance of success in many forms of acute ischaemic syndrome in the extremities, in segmental femoropopliteal thromboses not older than 6 to 8 weeks and in segmental occlusions of the pelvic arteries which can be of somewhat longer duration. Particularly good results can be expected when the indication is pelvic arterial stenosis due to large mural thrombi[1].

Systemic thrombolytic therapy, however, possesses an uncalculable risk of bleeding and, because of this, it has not been accepted universally. This risk of bleeding is perhaps somewhat less with urokinase, ultrahigh doses of streptokinase (9 million units within 6 hours)[2] or the relatively fibrin-specific gene-technologically produced tissue plasminogen activator (rt-PA)[3] but it still exists and, as with standard doses of streptokinase (a bolus of 250 000 units followed by 100 000 units/h for a maximum of 5 days), increases exponentially with the duration of treatment in every form of systemic thrombolysis.

A further disadvantage of systemic thrombolytic therapy is the long list of contraindications, to which embolic occlusion also belongs because of the risk of provoking further emboli. In contrast, with local thrombolytic therapy using very low doses of an activator there is certainly no risk of haemorrhage occurring or of new emboli being produced in the system so there are virtually no contraindications.

Streptokinase, urokinase and rt-PA are all very suitable for local thrombolysis of peripheral arterial occlusions. With total doses of up to 120 000 units of streptokinase and 50 mg rt-PA, systemic bleeding was observed in individual cases[4,5]; in over 700 treatments with 30 000 units of streptokinase, 100 000 units of urokinase or 2·5 mg rt-PA/h for a maximum of 3 h, no case of haemorrhage or embolization occurred[6]. This therapy imitates the process of spontaneous thrombolysis which is accomplished by means of the locally released tissue plasminogen activator synthesized in the vessel wall activating the plasminogen contained in the thrombus. Local thrombolytic treatment with rt-PA employs the same activator and therefore bears the closest resemblance to spontaneous physiological thrombolysis.

The principle of therapy is the systematic infiltration of the obstructing thrombus using a simple catheter which must have only one terminal opening and which is introduced percutaneously in the direction of the occlusion using the Seldinger technique. A continuous infusion of the activator in the above mentioned dose/h is commenced and at the same time under fluoroscopic monitoring the catheter is advanced centimeter by centimeter at intervals of 3 to 5 minutes until the distal open

Table 1 *Results of local low-dose thrombolytic therapy with streptokinase, urokinase and recombinant tissue plasminogen activator, rt-PA, in embolic and thrombotic peripheral arterial occlusions depending on their duration*

Type and duration of occlusion	Treatment	No. of occlusions	No. with primary recanalization	No. with recanalization lasting 2 weeks
Embolic				
>6 weeks	Streptokinase, urokinase	26	12	11 (42)
<6 weeks	Streptokinase, urokinase	66	54	48 (73)
<6 weeks	rt-PA	15	14	13 (87)
Thrombotic				
>6 months	Streptokinase, urokinase	102	51	37 (36)
<6 months	Streptokinase, urokinase	367	268	213 (58)
<6 months	rt-PA	61	53	49 (80)

Values in parentheses are percentages

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vessel is reached. If haemodynamically effective stenoses composed of material which is no longer lysable are still present, balloon catheter dilatation strictly limited to the segment involved is performed during the same session[6,7].

Early results of local thrombolytic treatment depend on the duration and type of occlusion. An embolic occlusion in a previously healthy artery apparently will lead to the organization of a thrombus more quickly than a thrombotic occlusion due to arteriosclerosis. A successful outcome lasting over 2 weeks can be expected in over 80 per cent of embolic and thrombotic occlusions existing for up to 6 weeks and 6 months respectively following the use of rt-PA (*Table 1*). The chance that these vessels remain open after 5 years is 89·5 per cent and 58·8 per cent for successfully treated embolic and thrombotic occlusions respectively[4].

Indications for local thrombolytic therapy are all femoropopliteal thrombotic and embolic occlusions existing for 6 to 8 months and 6 to 8 weeks respectively. Embolectomy remains the treatment of choice for embolic occlusions in the arteries of the arms, the abdominal aorta and the pelvic arteries including the common femoral artery and its bifurcation. One domain for local thrombolysis is thrombotic and embolic femoropopliteal occlusions including all arteries of the lower leg, particularly when critical ischaemia is present. Critical ischaemia is almost always due to a recent arterial occlusion which can be removed just as quickly by local thrombolysis as by vascular surgery.

An aneurysmal occlusion remains a contraindication for local thrombolysis as long as it can be satisfactorily treated primarily by vascular surgery. Where there is critical ischaemia with occlusion of all the arteries of the lower limb extending far into the periphery there is the chance, however, that local thrombolysis may be able to open up the affected vessel(s), thereby creating much more favourable starting conditions for the immediately subsequent surgical removal of the aneurysm.

Occlusions of femoropopliteal or femorocrural grafts can be dissolved for a period of several weeks after the onset and the majority of any existing anastomotic stenoses can be dilated during the same session. If there is persistently poor run-off local thrombolysis provides at least a patent transplant and often also allows better visualization of the outflow conditions which is an advantage for any subsequent reconstructive surgery.

Local thrombolytic therapy appears at first sight to be just another means of restoring arterial blood flow but indeed it is much more. It intervenes in the processes associated with the formation and progression of arterial occlusive disorders and leads to their regression, in rare cases back to almost the initial stages and in many cases for quite a considerable way. If rt-PA is used this is achieved in an almost physiological manner. Local thrombolytic therapy therefore provides a new method of quality in the treatment of arterial occlusive disorders.

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Association of Surgeons of Great Britain and Ireland

Br. J. Surg. 1990, Vol. 77, October, 1085–1090

A meeting of the Association of Surgeons of Great Britain and Ireland took place in Cardiff on 28–30 March 1990. The President of the Association, Professor Sir Herbert Duthie, was in the chair.

The Moynihan Prize was awarded to the authors of the following paper.

Bile acids and the increased risk of colorectal tumours after truncal vagotomy

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An association between colorectal cancer and previous peptic ulcer surgery is reported. In a prospective screening study, 100 asymptomatic patients (80 men and 20 women) who had undergone truncal vagotomy at least 10 years previously were investigated by barium enema, colonoscopy and gallbladder ultrasonography. Control data were obtained from forensic autopsy subjects. The incidence of neoplasms ≥1·0 cm in the vagotomized group was 14 per cent (11 adenomas, 3 carcinomas) and 3 per cent in controls (P=0·01). *Duodenal bile obtained at endoscopy from 21 vagotomized patients with normal gallbladders and from 21 control patients undergoing endoscopy was analysed by high performance liquid chromatography. The mean percentage of cholic (CA), chenodeoxycholic (CDCA), deoxycholic (DCA) and lithocholic (LCA) acids in the bile of vagotomized patients was 32·3, 45·6, 20·7 and 1·4 per cent respectively compared with 45·3, 36·2, 17·9 and 0·7 per cent respectively in controls. The increased proportions of CDCA and LCA and decreased proportions of CA in the duodenal bile of vagotomized patients were significant* (P<0·001; P=0·02; P=0·007). *Abnormalities in bile acid metabolism may help to explain the increased risk of colorectal neoplasia 10 years after truncal vagotomy.*

Keywords: Colorectal cancer, bile acids, vagotomy

Colorectal cancer is the second commonest cause of death from malignancy in the United Kingdom. Its prognosis is principally dependent on the extent of tumour spread at diagnosis. Duration of symptoms at the time of diagnosis, however, correlates poorly with survival[1]. Attention, therefore, has been directed towards presymptomatic detection and screening of high-risk groups[2]. Several retrospective studies have identified an increased mortality from colorectal cancer after surgery for peptic ulcer disease[3–7]. This association is controversial[8–10]. The overall risk appears to be increased twofold but may vary with the nature of the operation performed. A subgroup analysis reported a 9·5-fold excess risk in female patients treated by Billroth I gastrectomy and an eightfold excess mortality in females with duodenal ulcer treated by vagotomy[11].

Bile acids are suspected, from both clinical and experimental studies, to have a role in colon carcinogenesis[12]. It is suggested that the increased mortality from colorectal cancer after gastric surgery may be due to altered bile acid metabolism[4,6]. Data on the effect of vagotomy on bile acid metabolism are, however, conflicting[13–16]

The twofold increased mortality from colorectal cancer is apparent only 15–20 years after gastric surgery. It is reasonable to assume that the risks should be accompanied by an earlier increased prevalence of this form of cancer in gastric surgery patients. The aims of the present study were to determine the incidence of colorectal neoplasia in an asymptomatic population who had previously undergone truncal vagotomy and to identify any changes in duodenal bile acid profile which might be present following truncal vagotomy.

Patients and methods

Patients who had undergone truncal vagotomy for benign peptic ulcer disease at least 10 years previously were identified from Hospital Activity Analysis data and operation records Patients with symptoms already under investigation, those who had undergone revisional gastric surgery, cholecystectomy or enteric resection were excluded All those aged 50 years or older were invited to attend for double contrast barium enema examination and gallbladder ultrasonography These investigations were performed by consultant radiologists with a special interest in gastrointestinal investigation. Attention was given to the search for carcinomas or small polyps. Those with suboptimal barium studies or suspicious lesions underwent colonoscopy. Mucosal lesions were resected endoscopically and patients with carcinomas underwent appropriate operation. Following resection all lesions were examined histologically.

Since it was impractical and possibly unethical to obtain radiological studies in randomly selected normal individuals, control data were obtained from subjects undergoing forensic autopsy. In addition to formal autopsy the colorectum was opened, cleaned and examined for the presence of mucosal lesions. Hand-lens examination was not performed. The site and size of all mucosal lesions was noted and they were then excised and examined histologically. The presence or absence of gallstones was recorded. Those with a history of peptic ulcer surgery, cholecystectomy, colorectal neoplasia or enteric resection were excluded. As there is a disparity between the accuracy of autopsy and double contrast barium examination, only neoplasms 1 cm in diameter or larger were regarded as significant findings in this study.

Control subjects and patients were matched for sex, gallbladder status and as closely as possible for age (±5 years). The mean(s.d.) age of control subjects was 64·2(7·6) years. One hundred patients (80 men, 20 women), mean(s.d.) age 63·0(7·4) years, underwent double contrast barium enema and 35 had additional endoscopic examination of the colon.

Duodenal bile acids were analysed in 21 patients who had undergone truncal vagotomy. Patients with cholelithiasis on ultrasonography were excluded. There were 18 men and 3 women (mean(s.d.) age 61·4(7·0) years). Twelve patients had a pyloroplasty and nine a gastroenterostomy. Following an overnight fast patients underwent upper gastrointestinal endoscopy under intravenous sedation with midazolam. Residual duodenal juice was aspirated and discarded. Immediately after sedation, ceruletide (Farmitalia Carlo Erba, St. Albans, UK) was administered by slow intravenous injection to a maximum dose of 5 μg. When a flow of bile was observed, 5–10 ml of duodenal fluid was aspirated from close to the papilla of Vater and stored at −20°C until subsequent analysis by high performance liquid chromatography (HPLC). Control data were obtained from 21 age- and sex-matched individuals being investigated for dyspepsia and hiatus hernia. All vagotomy and control patients had normal gallbladders on ultrasound examination, were on normal diets and had normal bowel habit. None was taking medication likely to affect bile acid metabolism; in particular, none had taken antibiotics or laxatives for a month prior to investigation. The mean(s.d.) age of the control group was 57·9(14·2) years.

HPLC was used to determine the relative proportions of the principle primary and secondary bile acids in duodenal bile. The method used was based on that of Campbell *et al.*[17]. Separation of the unconjugated bile acids cholic (CA), chenodeoxycholic (CDCA), deoxycholic (DCA) and lithocholic (LCA) acids and their taurine (T) and glycine (G) conjugates was achieved in a single step over a period of 80 min. A 100 μl sample of a standard solution containing these 12 bile acids (500 ng each) was analysed before each batch of five specimens. This provided a standard chromatogram (*Figure 1a*) from which individual peaks in the specimen chromatogram (*Figure 1b*) could be identified and their concentrations calculated from the relative peak areas. The proportion of each bile acid present in the sample was then expressed as a percentage of the total bile acids identified. Sulphated bile acids were not detectable by this assay.

Bile acids were extracted from 100 μl samples of the duodenal aspirate by a solid phase extraction procedure using C18 Bond Elut cartridges (Jones Chromatography, Mid Glamorgan, UK) after the method of Swobodnik *et al*[18]. Samples were subsequently diluted (typically by a factor of 100) before analysis to ensure that peak areas fell within the linear range of the assay.

In order to determine the recovery rates and reproducibility of the assay, 500 ng of each of the 12 bile acids was added to 100 μl of bile sample, extracted and assayed using the HPLC method. Ten separate 100 μl aliquots of each 'spiked' bile sample were assayed in this way

Results

Of those invited to attend for screening 100 consented, 28 refused and 47 failed to respond. Twenty-six patients had cholelithiasis. Fifty-four patients had had a gastroenterostomy performed at initial vagotomy, the remainder having had a pyloroplasty. The mean(s.d.) interval from vagotomy was 16·3(3·8) years.

Of the 100 patients in the study group, 11 had adenomas 1 cm in diameter or larger. None exceeded 2 cm in size although one showed severe dysplasia. In addition, three male patients had established carcinomas. One man had synchronous hepatic flexure and sigmoid colon cancers and three large adenomas (*Table 1*). In this group of 14 patients with large adenomas or cancers (*Figure 2*), six had associated gallstones and eight had undergone gastroenterostomy as the drainage procedure. The post-vagotomy interval in patients with tumours was similar to that of the group as a whole.

The individuals in the control group, matched for age, sex and gallbladder status, died from causes listed in *Table 2*. Three subjects, all men, had a total of five adenomas 1 cm or larger, one of which was greater than 2 cm and severely dysplastic (*Figure 3*). One of these subjects had three large polyps. The incidence of large adenomas (≥1 cm) and cancers in the study group was significantly higher than in the controls ($P=0{\cdot}01$, χ^2 test).

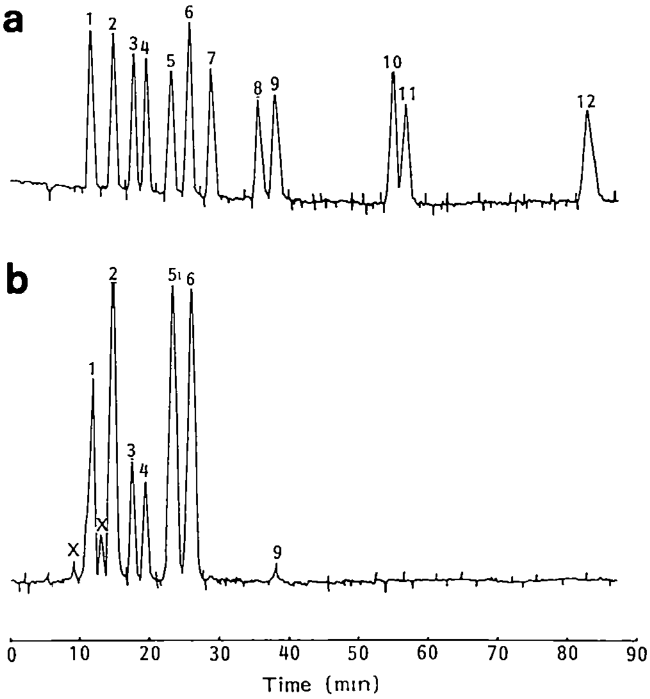

Figure 1 a *Standard chromatogram of 12 bile acids. Peaks 1–12 correspond to (1) TCA, (2) GCA, (3) TCDCA, (4) TDCA; (5) GCDCA; (6) GDCA, (7) TLCA, (8) CA, (9) GLCA, (10) CDCA; (11) DCA, (12) LCA (see text above for definitions of abbreviations),* **b** *Chromatogram showing separation of individual acids from a duodenal sample. X = unidentified peak*

Table 1 *Patients found to have malignant lesions*

Patient	Age	Sex	Gallbladder status	Operation	Tumour site	Stage
1	64	M	Cholelithiasis	TV+GE	Sigmoid	Dukes' A
2	62	M	Cholelithiasis	TV+GE	Hepatic flexure	Dukes' A
3	63	M	Cholelithiasis	TV+GE	Hepatic flexure Rectosigmoid	Dukes' A Dukes' C

TV+GE, truncal vagotomy and gastroenterostomy

In the HPLC analysis the limit of detection of each bile acid standard was 0·2 μg/ml. Calibration graphs were linear over the range 0·2–50 μg/ml for each individual acid. The mean(s.d.) recovery of unconjugated bile acids and their amidates from bile was 90·7(9·0) per cent (ten samples), range 82·9–98·1 per cent.

Differences were found in the composition of duodenal bile between vagotomized patients and controls (*Table 3*). There was an increase in the proportion of CDCA in the bile of vagotomized patients compared with controls, 45·6 per cent *versus* 36·2 per cent ($P<0{\cdot}001$, Wilcoxon sign rank test) and this was mainly due to a rise in the glycine fraction, 35·8 per cent *versus* 27·6 per cent ($P=0{\cdot}01$) (*Table 4*). The reciprocal decrease in the proportion of CA in vagotomized patients, 32·3 per cent *versus* 45·3 per cent was also significant ($P=0{\cdot}007$), and although both amidates were significantly reduced, the difference was again more marked in the glycine fraction, 24·2 per cent *versus* 34·3 per cent ($P<0{\cdot}001$). The proportion of LCA in the vagotomy group was significantly higher than in controls, 1·4 per cent *versus* 0·7 per cent ($P=0{\cdot}02$) although the proportion in both groups was small. The increase in DCA in vagotomized patients was not significant, 20·7 per cent *versus* 17·9 per cent ($P=0{\cdot}5$).

Table 2 *Causes of death in the autopsy control group*

Cause of death	No.
Coronary atheroma	39
Lung cancer	15
Miscellaneous respiratory diseases	8
Pneumonia	7
Aortic aneurysm	5
Drowning	4
Road traffic accident	3
Hypertension	3
Carbon monoxide poisoning	3
Pulmonary embolism	2
Valvular heart disease	2
Peritonitis	2
Subarachnoid haemorrhage	2
Miscellaneous	5

There was no difference in the duodenal bile acid profiles of patients with gastroenterostomy compared with pyloroplasty (*Table 5*).

Discussion

Decreased life expectancy after peptic ulcer surgery was reported over 30 years ago[19]. Renewed interest in this group of patients has highlighted their long-term predisposition to various forms of malignancy including lung, gastric and large bowel cancer[7,20].

This study reports an increased incidence of large (≥1 cm) adenomas and cancers in patients a decade or more after truncal vagotomy when compared with an age- and sex-matched control population. Colorectal cancer may be associated with

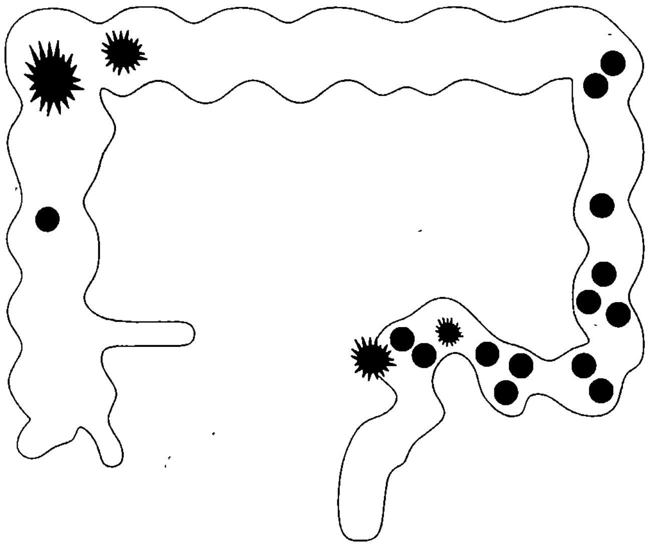

Figure 2 *Distribution of polyps ≥1 cm (●) and carcinomas (★) in the study group;* n=*14*

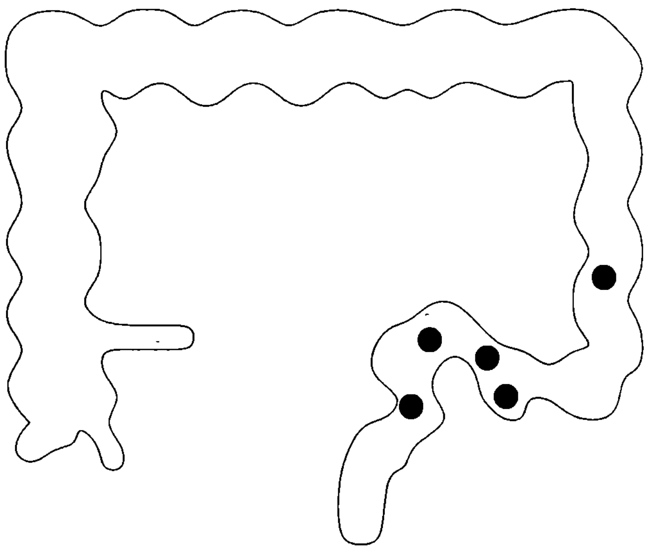

Figure 3 *Distribution of polyps ≥1 cm (●) in the control group;* n=*3*

Table 3 *Mean proportion (%(s.e.m.)) of bile acids in vagotomy group and controls*

	Cholic acid (CA)	Chenodeoxycholic acid (CDCA)	Deoxycholic acid (DCA)	Lithocholic acid (LCA)
Vagotomy group (*n*=21)	32·3(1·6)	45·6(2·2)	20·7(2·0)	1·4(0·3)
Control group (*n*=21)	45·3(1·9)	36·2(2·2)	17·9(2·1)	0·7(0·2)

Table 4 *Mean proportion (%(s.e.m.)) of bile acid amidates in vagotomy group and controls*

	TCA	GCA	TCDCA	GCDCA	TDCA	GDCA	TLCA	GLCA
Vagotomy group	7·9(1·1)	24·2(1·2)	9·8(1·2)	35·8(1·8)	4·4(0·5)	16·3(1·7)	0·2(0·1)	1·2(0·3)
Control group	10·9(0·9)	34·3(1·4)	8·6(0·8)	27·6(1·9)	4·0(0·6)	13·9(1·7)	0·0(0·0)	0·7(0·2)

Table 5 *Mean proportion (%(s e.m.)) of bile acids in pyloroplasty and gastroenterostomy patients*

	Cholic acid	Chenodeoxycholic acid	Deoxycholic acid	Lithocholic acid
Pyloroplasty group ($n=12$)	31·0(1·8)	44·7(2·9)	22·5(2·4)	1·8(0·5)
Gastroenterostomy group ($n=9$)	34·0(3·0)	46·9(3·7)	18·3(3·2)	0·8(0·2)

a history of cholecystectomy[21] or even cholelithiasis[22,23]. Although this association is controversial[24], we felt it important to match groups as far as possible for the presence of cholelithiasis. The prevalence of gallstones in this group (26 per cent) is consistent with the recent report by Mazzanti *et al.* of a high prevalence of gallstones in gastric surgery patients[25].

The twofold increased risk of death identified by Ross *et al.*[3] in a group of patients, 86 per cent of whom were treated by partial gastrectomy, was similar to that reported by Watt *et al.*[4] in a cohort of 735 patients treated by vagotomy, either truncal or selective. Very long-term follow-up (over 20 years or more) may be necessary before such mortality risks become apparent[7], but an increased prevalence of colorectal cancer should be apparent somewhat earlier. Our findings of an increased number of large adenomas and established cancers at a mean 16·3 years after surgery are consistent with this hypothesis. Contrary to these findings Toftgaard in an historical prospective cohort study[8] found no increased incidence of colorectal cancer in 4131 Danish patients treated surgically for benign peptic ulceration and followed up by computerized record linkage for a mean of 17·15 years. He considered the increased (observed/expected = 1·4) risk of colorectal cancer after 20 postoperative years to be artefactual, but felt his conclusions were less valid for vagotomy patients who constituted only 0·9 per cent of the cohort. This Danish study contained a significant number of patients (14·5 per cent) whose simple suture of perforated ulcer cannot be expected to have had significant long-term pathophysiological consequences.

The 1·6-fold increase in mortality from colorectal cancer 20 or more years after gastric surgery in patients at St. James Hospital, Balham[11] was almost entirely due to a 9·5-fold excess risk in female gastric ulcer patients treated by Billroth I gastrectomy and an 8·0-fold excess risk in females with duodenal ulcer treated by vagotomy. While these results broadly support the findings of the present study, they must be interpreted with caution based as they are on relatively small subgroups. Bundred *et al.*[6] in a matched case-controlled study found that 27 of 289 patients with colorectal cancer had previous gastric surgery compared with 13 of 289 age- and sex-matched controls. In a similar but larger study Kune *et al.*[10] found no association between colorectal cancer and previous gastric surgery for peptic ulcer in an Australian population.

Although it is recognized that autopsy subjects constitute a select group of controls, we believe that our controls (*Table 2*) broadly represent the average population. Their deaths were notified to the Forensic Service because they were thought not to be due to natural causes or because they had not been treated by a medical practitioner within the preceding 28 days. It is unlikely that these selection factors could influence the incidence of adenomatous polyps which were coincidental findings not related directly to the causes of death.

Nevertheless the 3 per cent incidence of large adenomatous polyps in our control group is low compared with most autopsy series from high-risk areas[26–28]. This may be partly explained by the relatively low mean age of our series (64 years). The 3 per cent incidence is remarkably similar to that in a previous separate study from the same community[29] and consistent with a recent clinical report[30] showing a 3 per cent incidence of large polyps (> 1 cm) in asymptomatic patients screened by 100 cm colonoscopy. Farrands and Hardcastle[31] found only one patient with adenomatous polyps amongst 128 'symptomatic' patients (0·8 per cent) screened by double contrast barium enema and/or flexible sigmoidoscopy. Grossman and Milos[32] found only one polyp > 9 mm above the rectosigmoid junction in 154 patients (0·6 per cent) with a family history of colorectal cancer screened by total colonoscopy. Above the level of rigid sigmoidoscopy they estimated the prevalence of advanced neoplasms (tubular adenomas > 10 mm; tubulovillous, villous or severely dysplastic adenomas; cancers) to be 3 per cent in an average population, mean age 62·8 years[33]. One might, of course, expect the detection rates in clinical studies to be somewhat lower than in autopsy series, even for large polyps.

The detection rate, particularly of invasive malignancy, in our screened group is much higher than might be expected in an asymptomatic group at no apparent increased risk of colorectal cancer. Even in autopsy series the number of incidental colorectal malignancies rarely exceeds 1 per cent when very elderly patients are excluded[26–28]. The high proportion of Dukes' A lesions detected is in keeping with an asymptomatic screened population. The 14 per cent detection rate of significant lesions in our asymptomatic population approaches that found by Jensen *et al.*[34] in faecal occult blood positive patients (adenomas ⩾ 1 cm 12·6 per cent, cancer 5 per cent). Bertario *et al.*[35] found an 8·6 per cent incidence of adenomas ⩾ 1 cm and a 1·7 per cent incidence of new cancers in a slightly younger group of patients but all of whom were at increased risk of colorectal cancer.

Outpatient double contrast barium enema cannot be considered the optimal method of screening a potentially high-risk group but we were aware of its relative acceptability in our community compared with inpatient colonoscopy. The initial acceptance rate of 57 per cent was high and reduces the potential for self-selection bias. Concern over the method of screening should not detract from the results since this radiological investigation is likely to underestimate the true incidence of neoplasia in the study group.

It would be incorrect to conclude from this study that vagotomy *per se* either initiates or promotes colorectal cancer although an explanation for the assocation is required. Abnormalities of bile acid metabolism have been suggested as a cause of the reported increased incidence of colonic cancer after cholecystectomy[36]. Bundred *et al.*[6] speculated that similar alterations in faecal bile acids after vagotomy and drainage might explain the increased incidence of colorectal cancer after peptic ulcer surgery. Data on the effect of truncal vagotomy on bile acid metabolism are conflicting. The increase in bile acid pool size[14,16,37] after vagotomy might be expected to alter bile composition[38]. Allan *et al.*[39] found an increased faecal excretion of CDCA in vagotomized patients but in his small group of patients this was only significantly higher than control values in those with post-vagotomy diarrhoea. Other investigators, however, have found no alteration in bile composition after vagotomy[15,40]. The abnormalities of duodenal bile acid profile noted in this study are similar to those reported in a separate study from our group by Moorehead *et al.* in the duodenal bile of patients with adenomatous polyps and colorectal cancer[41].

The reason for a reversal in the normal ratio of primary bile acids in duodenal bile is unclear as is its significance in colorectal carcinogenesis. CDCA is metabolized to LCA by bacterial dehydroxylation in the colon. An increased proportion of CDCA in duodenal bile is in keeping with Owen's findings of an increase LCA:DCA ratio in the faeces of patients at risk of colorectal cancer[42,43]. We have no direct evidence, however, that the changes in duodenal bile acids in our study are reflected in abnormal faecal bile acid profiles. The changes in the proportion of CA and CDCA in vagotomy patients were predominantly due to alterations in their glycine fraction. In most individuals amidation is predominantly with glycine but the mechanisms for determining the relative proportions of glycine and taurine amidates are poorly defined. The reasons for more marked alteration in the glycine conjugates is unexplained. The mean proportions of LCA detected in this study were very small in both groups and we are reluctant to draw any conclusions from the apparent increase in LCA in the bile of vagotomy patients. Following amidation much of the LCA is sulphated during hepatic transport and does not circulate enterohepatically. The assay used in this study was unable to detect sulphated LCA, and since the degree of sulphation may vary widely not only between individuals but also with time, further data are required to assess the significance of this result. There is evidence that gastroenterostomy and pyloroplasty have different effects on intraluminal bile acid concentrations[44]. There was no significant difference in the composition of duodenal bile between those patients with gastroenterostomy and those with pyloroplasty but all three post-vagotomy patients with established cancers in our study had undergone gastroenterostomy.

Duodenal bile acid analysis provides a qualitative assessment of the composition of the bile acid pool. Variable and indeterminable dilution of bile with duodenal and pancreatic secretion precludes quantitative analysis. Quantitative studies are required to confirm the qualitative abnormalities we have detected and, in particular, it is necessary to establish whether these changes in the duodenal bile acid profile are reflected in the faecal bile composition in similar individuals. In addition, other consequences of vagotomy which might influence mucosal proliferation such as hypergastrinaemia, altered calcium metabolism and intraluminal pH, merit further investigation.

The importance of colorectal cancer in peptic ulcer surgery patients must be kept in perspective. Only 4 per cent of the Edinburgh[3] and Belfast[4] cohorts actually died from this form of cancer, the vast majority of deaths being attributable to smoking-related diseases. These mortality studies tend to underestimate the potential morbidity since more patients develop colorectal cancer than actually die from it In our study three asymptomatic cancer patients were identified, all potentially curable. These results suggest that post-vagotomy patients might benefit from colorectal screening. Large prospective truncal vagotomy follow-up studies, even if feasible, could take 15–20 years to show any increased prevalence of colorectal neoplasms. Useful information might be obtained from further historical prospective cohort studies[8] provided accurate record linkage identified patients who develop colorectal neoplasms. It is also important to establish whether patients who have undergone proximal gastric vagotomy are also at risk of colorectal cancer. Furthermore H_2-receptor antagonists have only been available and prescribed in vast quantities in the past 10 years[45]. It is too soon to assert that these patients do not carry the same long-term risks which this study has identified in their surgical counterparts.

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Urinary tissue factor activity in colorectal disease

Procoagulant activity (PCA) in normal urine has been recognized for over 50 years. Although tissue factor (TF) is produced by certain tumours, and is increased in both tumour-associated macrophages and blood monocytes, the possibility that it might also be increased in urine has not been studied in patients with cancer. We have measured urinary PCA in hospital controls without inflammatory or neoplastic disease (n = *79*)*, in patients with rheumatoid arthritis* (n = *8*)*, inflammatory bowel disease* (n = *19*)*, colorectal cancer* (n = *70*) *and in patients undergoing colonoscopy* (n = *50*)*. Urinary PCA was higher* (P < *0·001*) *in patients with colorectal cancer and inflammatory bowel disease than controls or patients with rheumatoid arthritis. Fourteen (88 per cent) out of 16 colonoscopy patients subsequently found to have carcinoma or inflammatory bowel disease had levels above the control upper quartile, compared with 8 (24 per cent) out of 34 with normal colonoscopy* (P < *0·001*)*. TF inhibitors confirmed the nature of the PCA and Western blotting studies indicated a urinary TF molecular weight of approximately 38 000. These studies provide further evidence of abnormal haemostasis in malignancy and suggest that determination of urinary TF may provide a useful screening test in patients undergoing colonoscopy.*

Keywords: Cancer, coagulation factors, tissue factor, urine

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Urine has long been known to contain a 'thromboplastic' substance that normalizes the clotting time of haemophiliac plasma[1]. There is no known role for urinary procoagulant activity (PCA), although it is thought to explain the clot colic occasionally experienced by haemophiliacs[2]. Urinary PCA was initially defined by the ability of urine, in the presence of lipid, absorbed bovine plasma (providing factor V) and calcium ions, to activate prothrombin[3]. This assay system will not detect true tissue thromboplastin[4], and is more likely to measure a prothrombinase-like activity. This type of urinary PCA displayed remarkable heat stability, losing only 30 per cent of its activity at 100°C for 15 min[5] and, in further contrast to tissue factor, the active substance contained a high proportion of sulphur, but no phosphorus[6].

Other investigators have reported a different type of procoagulant. Using a recalcified clotting assay, Joist and Alkjaersig identified a urinary factor that required clotting factors VII and X for its activity[7]. PCA was low in patients with parenchymatous renal disease and was not elevated in five out of six patients with advanced malignancy The nature of this urinary procoagulant has not been fully established.

Abnormalities in the coagulation system are frequently associated with disease[8], and can be related to procoagulant activities of both tumour and host cells. Amongst human tumours, gastric[9], ovarian[10] and renal carcinoma[11] produce increased amounts of tissue factor (TF), as do tumour-associated macrophages[12] and the peripheral blood monocytes of patients with cancer[13] and inflammatory bowel disease[14]. The possibility that urine TF activity may also be increased in malignancy has not previously been explored. The aims of the present study were, therefore, to measure urinary PCA in patients with both cancer and inflammatory disease of the colon, to compare the results with hospital controls and patients with rheumatoid arthritis, and to characterize the PCA using appropriate biochemical inhibitors and Western blotting.

Patients and methods

Patients

A total of 226 subjects were studied and divided into five groups. (1) hospitalized control patients (*n* = 79) on surgical wards, excluding those with inflammatory or neoplastic disorders; (2) patients with proven inflammatory bowel disease (*n* = 19), (3) patients with colorectal carcinoma (*n* = 70); (4) patients about to undergo colonoscopy (*n* = 50); and (5) patients with active (erythrocyte sedimentation rate > 70 mm/h) rheumatoid arthritis (*n* = 8).

Assay of urinary procoagulant activity

Early morning urine samples, collected into sterile universal containers, were analysed on the morning of collection, since in preliminary experiments (data not shown) the procoagulant activity showed relatively poor stability. Samples were centrifuged at 2000*g* for 10 min and the supernatant used for assay of procoagulant activity as described below.

The assay system used to measure urinary procoagulant was a chromogenic assay, designed to detect TF and TF-like activity In principle, urinary procoagulant, in the presence of factor VII and calcium ions, activates purified factor X. The activated product specifically converts a chromogenic substrate from a colourless to a yellow form which can be measured spectrophotometrically TF assays were performed in 96-well flat-bottomed microtitre plates. Each well contained 40 μl assay buffer (0·05M Tris-HCl, pH 7·8), 20 μl $CaCl_2$ (0·025M), 20 μl urine sample and 20 μl (1 unit/ml) partial human prothrombin complex (Prothromplex TIM4, Dunton Green, UK) as a source of factors VII and X. Blank wells for each sample contained the above mixture with 20 μl assay buffer in place of Prothromplex The reagents were then incubated for 30 min at 37°C. Factor Xa generation was stopped by adding 100 μl of ethylene diamine tetraacetic acid (7·5 mM in assay buffer); 40 μl chromogenic substrate (CBS 31·39, Diagnostica Stago, France) was added and incubation continued for 45 min at 37°C. Colour development was then terminated with 50 μl glacial acetic acid and absorbances measured at 410 nm on a Dynatech MR700 (Dynatech Laboratories Ltd., Billinghurst, UK) plate reader. Preliminary experiments had already ensured that the reaction was

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Table 1 *Urinary procoagulant activity in tissue factor (TF) units of hospital controls, patients with rheumatoid arthritis, inflammatory bowel disease, colorectal cancer and subjects undergoing colonoscopy*

Patient group	No. of patients	TF units Median	TF units Interquartile range	*P**
Controls	79	17·1	11·2–27·7	–
Rheumatoid arthritis	8	15·1	9·7–26·9	n.s
Inflammatory bowel	19	58·9	33·4–68·5	<0·001
Colorectal cancer	70	49·0	32·2–66·2	<0·001
Colonoscopy	50	27·0	18·0–49·2	–

* Significance relative to hospital controls (Mann–Whitney *U* test)

linear over the range of activities encountered in this study. Absorbance values were converted to TF units using a calibration curve constructed from dilutions of commercially available human placental thromboplastin (Thromborel S™, Behring, Hounslow, UK). A 1/500 dilution of the stock material, which gave a one-stage prothrombin time of 49 s with normal plasma, was arbitrarily assigned a value of 400 units.

The effect of biochemical inhibitors of tissue factor

A variety of agents, known to be inhibitors of TF activity, were preincubated with urine samples before procoagulant assay as detailed above:

1. 6·6 μl of a goat antibody to human TF (kindly provided by Dr L. V. M. Rao, San Diego) was added to 193 μl urine and the mixture incubated at 37°C for 15 min. Aliquots of the mixture were then assayed for procoagulant activity as normal. As a control for non-specific interference with the assay by immunoglobulin, rabbit anti-human prothrombin (Dako Ltd., High Wycombe, UK) was similarly incubated with the urine samples. 12 μl prothrombin antibody was mixed with 188 μl urine, such that the final concentration of immunoglobulin protein was the same in both antibody studies.
2. 20 μl of concanavalin A (Sigma, Poole, UK) (1 mg/ml in distilled water) was added to 180 μl urine. The mixture was incubated at 37°C for 60 min before assay for procoagulant activity.
3. 3·3 μl of phospholipase C (Sigma), at a concentration of 100 units/ml, was added to 180 μl urine (1.55 v/v). The mixture was incubated at 37°C for 60 min before assay for procoagulant activity.

Western blotting

40 ml urine was centrifuged at 2000*g* for 20 min to remove insoluble debris. The supernatant was recentrifuged at 50 000*g* for 1 h. The pellet was then resuspended in 0·5 ml 0·15 M NaCl and subjected to sodium dodecyl sulphate–polyacrylamide gel electrophoresis on a 10 per cent polyacrylamide gel[15]. After electrophoresis the separated proteins were transferred electrophoretically from the polyacrylamide gel to nitrocellulose sheets[16]. Each urine sample was electrophoresed in duplicate, one lane of each pair was then stained with Coomassie Brilliant Blue to visualize the protein bands, while any TF present on the nitrocellulose sheet was then specifically localized with the same anti-TF antibody used in the inhibition studies described above. The immobilized anti-TF was subsequently visualized with alkaline phosphatase-conjugated anti-IgM[17]. This procedure enabled the molecular weight of urinary TF to be determined by comparing the position of labelled bands with those of standard proteins of known molecular weight. A sample of commercially-available brain thromboplastin (Diagnostics Reagents Ltd., Oxfordshire, UK) was tested in parallel.

Statistical analysis

Data analysis was performed using the STATGRAPHICS™ (STSC Inc., Rockville, USA), Statistical Graphics System. The results were not normally distributed and were therefore expressed as median and interquartile ranges. Differences between groups were assessed with the Mann–Whitney *U* test. Throughout this work, $P<0·05$ was taken to indicate statistical significance.

Results

The control group displayed generally low urinary TF levels, with a fairly narrow range of activity (*Table 1*). Patients with inflammatory bowel disease and colorectal carcinoma, however, had significantly higher levels of urinary procoagulant than the control group ($P<0·001$). There was no difference between the inflammatory bowel disease and colonic cancer groups or between subjects with rheumatoid arthritis and the control group. Ninety-four per cent of the patients with inflammatory bowel disease and 85 per cent of those with colorectal carcinoma had urinary TF activity above the upper quartile for the control group.

Following histological assessment, the colonoscopy patients were subdivided into two subgroups. In some patients, histological examination following colonoscopy revealed no abnormality of the large bowel, while in others significant pathology (inflammatory bowel disease or carcinoma) was disclosed. Of these patients, eight (24 per cent) out of 34 with a normal colonoscopy had a urinary procoagulant activity above the upper quartile of the control group, while 14 (88 per cent) out of 16 with an abnormal colonoscopy had an elevated level by the same criteria ($P<0·001$, χ^2 test). The group with a normal colonoscopy did not differ from controls, while those with an abnormal colonoscopy had a significantly higher urinary procoagulant activity ($P<0·001$). The difference between the two groups of colonoscopy patients is illustrated in *Figure 1*.

Incubation of urine with a goat antibody to human TF reduced the procoagulant activity of the test samples ($n=16$) by over 90 per cent; the mean(s.d.) residual activity was 15·2(8·2) per cent. After incubation with the same amount of anti-prothrombin IgG, the activity was 93·3(12·8) per cent of the original ($n=9$). This loss of activity was not statistically significant. Urinary procoagulant activity was also significantly reduced ($P<0·001$) by concanavalin A, 34·5(8·5) per cent, and phospholipase C, 17·0(6·1) per cent. These results are illustrated in *Figure 2*.

The results of Western blotting are shown in *Figure 3*. Blots from a normal subject (lane B) and from two patients with cancer (lanes C and D) showed a band staining for TF at the same position as the thromboplastin control (lane A) and an additional band of higher molecular weight. Comparison with the standard molecular weight marker proteins (lane E) yields estimates for the molecular weight of the urinary TF components of 38 000 and 66 000. Subsequent experiments (data not shown) revealed that the higher molecular weight band could be removed by immunoaffinity adsorption of the

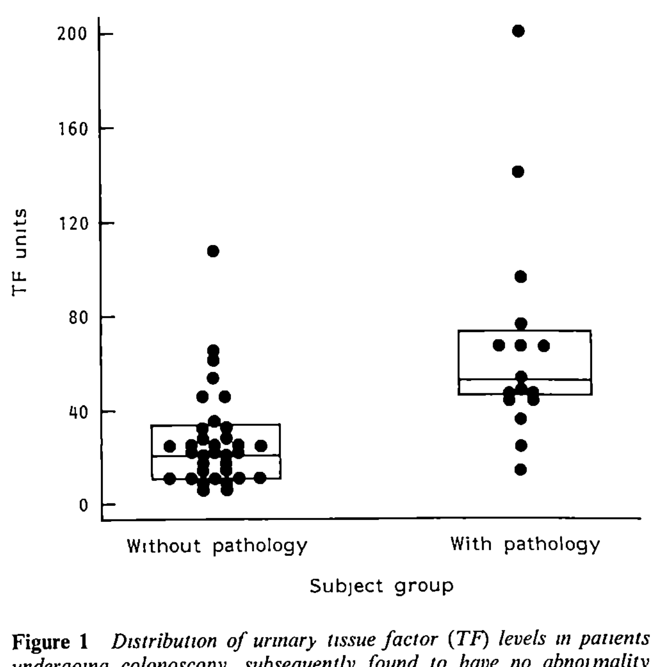

Figure 1 *Distribution of urinary tissue factor (TF) levels in patients undergoing colonoscopy, subsequently found to have no abnormality* (n = *34*) *or significant pathology (inflammatory bowel disease or carcinoma,* n = *16*) *The boxes enclose the interquartile ranges and the central lines denote the median*

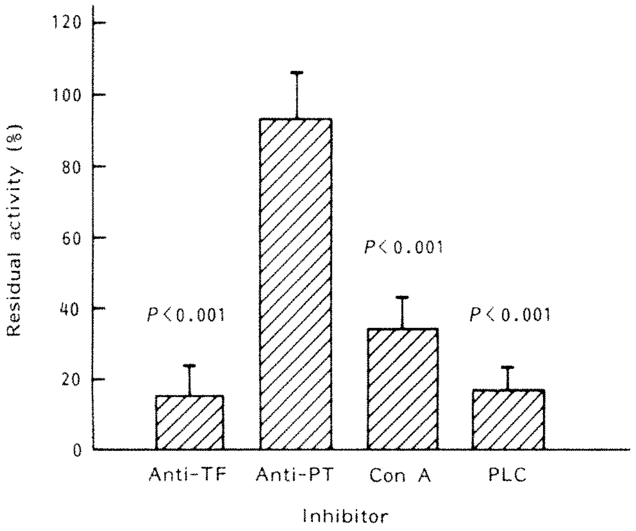

Figure 2 *Effect of anti-tissue factor (anti-TF), anti-prothrombin (anti-PT), concanavalin A (con A) and phospholipase C (PLC) on urinary procoagulant activity. Results are expressed as the mean(s.d.) percentage of the initial activity.* P *values were obtained by comparing the pre- and post-treatment TF levels (paired Student* t *test)*

urine sample on an anti-human albumin column. This suggests that the 66000 band represents TF which was non-specifically bound to albumin.

Discussion

Monocyte TF expression is often increased in malignant disease. We have recently shown that the procoagulant activity of endotoxin-stimulated whole blood is greater in patients with colorectal or breast tumours than in normal or benign controls, and is also increased in inflammatory bowel disease[18]. This latter finding agrees with the observation that isolated monocytes from patients with Crohn's disease have increased monocyte TF activity which correlates with intravascular clotting changes and disease activity[14].

The present study has demonstrated elevated levels of procoagulant activity in the urine of patients with colorectal cancer and inflammatory bowel disease compared with control hospital patients. These results appear to parallel those obtained in our earlier study of whole blood procoagulant activity[18]. The demonstration of raised urinary TF levels cannot be used to distinguish between inflammatory and malignant bowel disease, and the possibility that increased urinary TF may be part of an acute phase reaction cannot be entirely excluded on the basis of the present study. However, it is noteworthy that subjects with rheumatoid arthritis, all of whom had active disease, had generally normal levels. Whether the measurement of urinary procoagulant activity might be useful in the detection of other types of malignancy remains to be established; it has previously been shown that levels are higher in patients with breast cancer than in those with benign breast disease[19].

That urinary procoagulant activity is elevated in both cancer and inflammation of the large bowel may have useful diagnostic implications. This test might be used as a 'screening' procedure for patients with symptoms of large bowel disease to determine whether urgent colonoscopy is indicated, and to select patients in whom colonoscopy may, or may not, be more appropriate than barium enema examination.

The present data have confirmed that urinary procoagulant activity is due to TF by demonstrating almost total inhibition of procoagulant activity with a specific antibody to human TF. An equivalent amount of anti-prothombin IgG, however, had virtually no effect. This indicates that the inhibitory effect of anti-TF was not simply due to non-specific interference of immunoglobulin with the assay and confirms that 'prothrombinase' activity did not significantly contribute to cleavage of the chromogenic substrate. Pre-incubation of urine samples with two other known inhibitors of TF also markedly reduced their procoagulant activity. Concanavalin A is a lectin that binds to the saccharide groups of TF and inhibits its action[20], while phospholipase C cleaves the phospholipids essential for TF activity[21]. The effects of these agents provide additional evidence of the identity of the urinary procoagulant. Although concanavalin A has already been shown to inhibit urinary procoagulant[22], the effects of the other agents have not previously been tested. Other workers have assumed that urinary procoagulant was TF by its mode of participation in the blood coagulation mechanism; urinary procoagulant could not substitute for factors VII or X in a clotting assay[7] and accelerated the factor VIIa-catalysed activation of factor X[23].

Previous workers have obtained varying estimates of the molecular weight of urinary procoagulant. The 'purified' protein was thought to exist in macroaggregates of molecular weight of over 20 million[22], within which were basic functional units of molecular weight 151000. These separated, under reducing conditions, into components of molecular weight 78000 and 68000. In the present study gel electrophoresis was performed on unpurified urine samples, thereby eliminating potential artefacts introduced during separation procedures, and TF visualized specifically by Western blotting. The results of these experiments allow two conclusions to be drawn. Firstly, although only present in small

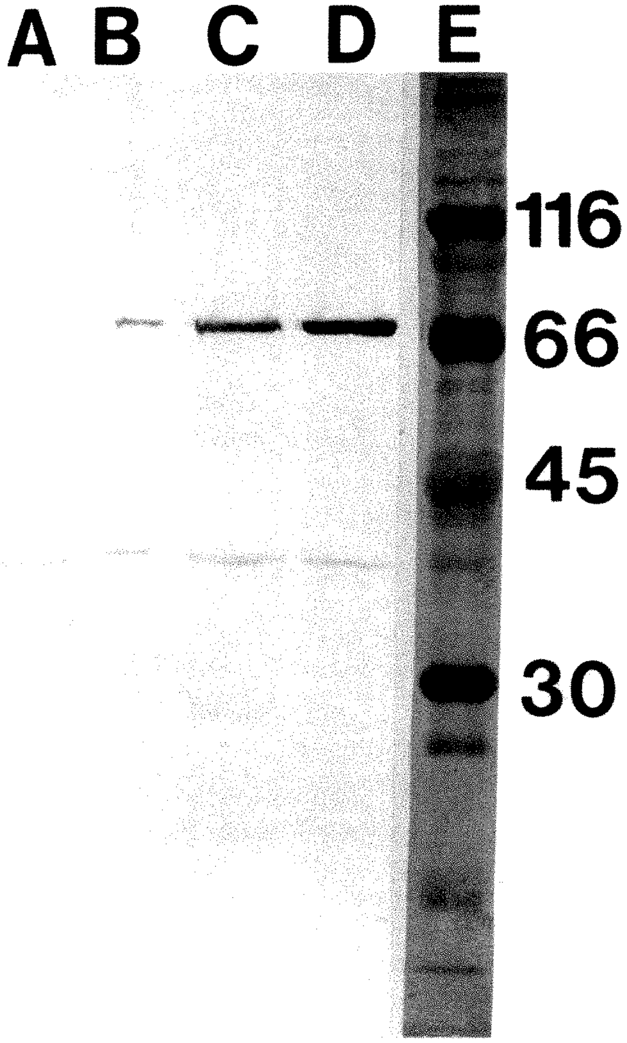

Figure 3 *Western blot of brain thromboplastin (lane A), urine from a healthy subject (lane B) and urine from two cancer patients (lanes C and D) visualized with anti-tissue factor. Lane E represents a blot of marker proteins of the indicated molecular weights (marked in 1000s) stained with Coomassie Brilliant Blue for comparison*

amounts, a protein antigenically identical to TF was present in unfractionated urine. This represents direct and unequivocal evidence that urine contains TF. Secondly, this approach showed the molecular weight of urinary TF to be approximately 38 000, the higher molecular weight band probably representing tissue factor bound to albumin. In comparison, human brain TF has a molecular weight of 43 000–45 000[24,25]. TF from various tissues (fat, placenta, adrenal gland, small intestine, kidney and umbilical vein) is encoded by the same gene[26]. This gene predicts a 293 chain amino acid of molecular weight 30 000, the difference between this and the observed molecular weight of TF being accounted for by glycosylation. Given that TFs from a variety of sources have the same amino acid structure, it is possible that the small difference in the molecular weight of brain and urine TF is due to differences in glycosylation, or partial degradation of the urinary protein by proteases in the urine.

The source of urinary tissue factor remains unclear. Its level is reduced in renal disease, suggesting production by the kidney[7], a theory supported by immunolocalization studies[27]. Although the level of urinary procoagulant appears to parallel that of whole blood and monocyte TF activity in both neoplastic and inflammatory bowel disease, it is unlikely that the urinary factor is derived from the peripheral blood since it is too large a molecule to pass through the undamaged glomerular basement membrane. It seems more likely that either renal macrophages or glomerular cells themselves become 'activated' in malignant states and certain inflammatory diseases – possibly by the same unidentified factors that stimulate blood monocytes – to secrete TF.

The importance of using TF activity as a marker of colorectal malignancy and inflammatory disease requires further study. We are at present determining the sensitivity and specificity of elevated urinary TF as a screening test for colorectal pathology. In addition, the effects of such variables as age, sex, exercise and smoking must be evaluated before the measurement of urinary TF could be used as a clinical test.

In summary, this study has yielded several new observations about urinary procoagulant. Human urine contains a procoagulant that is present at relatively low levels in the urine of hospital controls and patients with rheumatoid arthritis. Urine procoagulant activity is higher in patients with inflammatory bowel disease and colorectal carcinoma, and studies on patients undergoing colonoscopy indicate that this test may be a useful marker of colorectal pathology. Biochemical characterization confirmed that the urinary procoagulant is identical to TF, and has a molecular weight similar to that of TF from other sources.

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Intraoperative air testing of colorectal anastomoses: a prospective, randomized trial

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A total of 145 consecutive patients receiving a colorectal anastomosis were randomized to 'test' or 'no test' once the anastomosis had been completed. Anastomotic testing was performed with the pelvis filled with saline and the rectum distended by sigmoidoscopic insufflation of air. Any leaks demonstrated were oversewn. A water-soluble contrast enema was performed on the tenth postoperative day. Seventy-four patients were randomized to 'test' and 71 to 'no test' but one patient was withdrawn from each group leaving a total of 143 for analysis. The two groups were well matched for age, sex, diagnosis and operative details. Eighteen (25 per cent) air leaks were detected and repaired in the 'test' group. After operation there were three (4 per cent) clinical leaks in the 'test' group and ten (14 per cent) in the 'no test' group (Fisher's exact test, P=*0·043). There were eight (11 per cent) radiological leaks in the 'test' group and 20 (29 per cent) in the 'no test' group* (P=*0·006). Intraoperative air testing and repair of colorectal anastomoses significantly reduces the risk of postoperative clinical and radiological leaks.*

Keywords: Colorectal surgery, anastomosis, leak, test

Anastomotic leakage is the most significant complication of colorectal surgery and is the commonest cause of postoperative mortality[1]. Many causative factors have been implicated but the most important appears to be surgical technique[2]. Two small studies have suggested that intraoperative testing of colorectal anastomoses might reduce postoperative leakage by permitting the detection and repair of any defects[3,4].

This prospective, randomized study was performed to establish whether intraoperative testing could reduce the incidence of postoperative leakage following colorectal surgery.

Patients and methods

One hundred and forty-five consecutive patients receiving a colorectal anastomosis were entered into the study. Two patients were subsequently withdrawn leaving 143 for analysis. Elective and acute procedures performed by consultants and trainees at all three Leicester hospitals were included. There were 78 men and 65 women with a median age of 69 years (range 35–92 years). Ninety-six (67 per cent) operations were for elective resection of a carcinoma, 15 (10·5 per cent) for diverticular disease, 15 (10·5 per cent) for an obstructive carcinoma and 17 (12 per cent) for reversal of a previous Hartmann's procedure.

Picolax® (Nordic, Feltham, UK) was used for bowel preparation except for those in which obstruction was present. Antibiotic prophylaxis, consisting of intravenous cefuroxime 1·5 g and metronidazole 500 mg at induction of anaesthesia, was routinely employed. All operative decisions were left to the operating surgeon who was a consultant in 52 (36 per cent) and a trainee in the other 91 (64 per cent). Eighty-two (57 per cent) anastomoses were hand-sutured by a variety of techniques and the other 61 (43 per cent) were stapled. Seventy-two (50 per cent) anastomoses were above the peritoneal reflection, 50 (35 per cent) were below the peritoneal reflection and 21 (15 per cent) were very low anterior resections. These were also performed using the double-stapler technique of a linear Roticulator® to close the rectal stump and a circular Premium CEEA® to complete the anastomosis (Auto Suture, Ascot, UK). A pelvic suction drain was always used and a transverse defunctioning colostomy fashioned in 18 (13 per cent) patients.

After completion of the anastomosis the patients were randomized to 'test' or 'no test' by opening a sealed envelope. Air testing was performed by inserting a sigmoidoscope into the anal canal. A soft clamp was placed across the bowel above the anastomosis with the pelvis filled with saline. Air was insufflated until the rectum was distended and any leakage detected by the bubbles arising from it (*Figure 1*). If a leak occurred it was oversewn and retested until secure.

After surgery, any evidence of a clinical leak in either group was recorded and a limited water-soluble contrast enema performed on the tenth postoperative day. The contrast studies were reported by a radiologist who was unaware of the randomization protocol. Statistical comparison of the two groups was by the Mann–Whitney U test for age and the χ^2 test for all other factors. Analysis of the results of air testing was by Fisher's exact test.

Results

Of the 145 patients originally entered into the study, 74 were randomized to 'test' and 71 to 'no test'. Two patients were subsequently withdrawn leaving 143 for analysis (73 'test' and 70 'no test'). The patient withdrawn from the 'no test' group died fom a myocardial infarction on the first postoperative day.

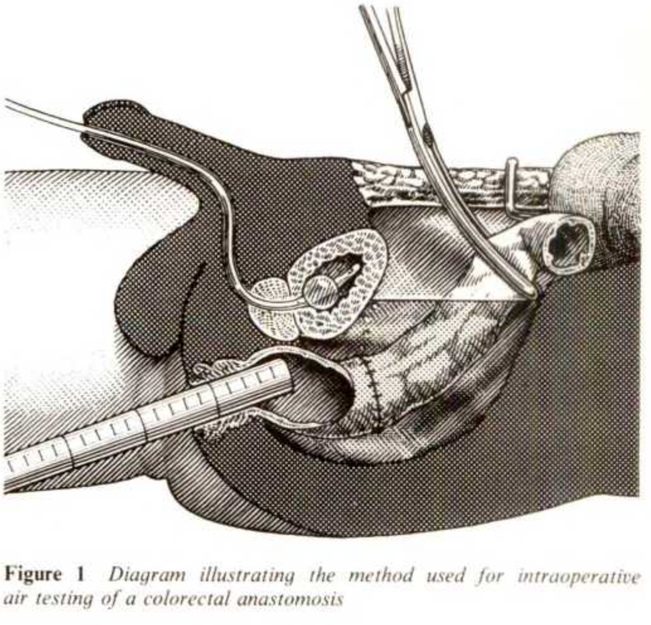

Figure 1 *Diagram illustrating the method used for intraoperative air testing of a colorectal anastomosis*

Table 1 *Comparison of the 'test' and 'no test' groups*

	Group	
	Test	No test
No. of patients	73	70
Age, median and range, in years	67, 41–92	69, 35–90
Men	42 (58)	36 (51)
Sutured anastomosis	38 (52)	44 (63)
Covering colostomy	10 (14)	8 (11)
Consultant surgeon	25 (34)	27 (39)
Indication for operation		
Elective carcinoma	50 (68)	46 (66)
Diverticular disease	9 (12)	6 (9)
Obstructing carcinoma	7 (10)	8 (11)
Reversal of Hartmann's procedure	7 (10)	10 (14)
Level of anastomosis		
Above peritoneal reflection	37 (51)	35 (50)
Below peritoneal reflection	24 (33)	26 (37)
Very low anterior resection	12 (16)	9 (13)

Values in parentheses are percentages

Table 2 *Comparison of the postoperative 'leak' and 'no leak' groups (clinical and radiological combined)*

	Group	
	Leak	No leak
No. of patients	32	111
Age, median and range, in years	70·5 (52–83)	68 (35–92)
Men	21 (66)	57 (51)
Sutured anastomosis	18 (56)	64 (58)
Covering colostomy	4 (12)	14 (13)
Consultant surgeon	14 (44)	38 (34)
Indication for operation		
Elective carcinoma	21 (66)	75 (68)
Diverticular disease	5 (16)	10 (9)
Obstructing carcinoma	4 (13)	11 (10)
Reversal of Hartmann's procedure	2 (6)	15 (14)
Level of anastomosis		
Above peritoneal reflection	11 (34)	61 (55)
Below peritoneal reflection	12 (38)	38 (34)
Very low anterior resection	9 (28)	12 (11)

Values in parentheses are percentages unless otherwise stated

The other withdrawal, in the 'test' group, had an air leak from a low anterior resection which could not be repaired. A transverse defunctioning colostomy was performed and the patient made an uneventful recovery. The two groups were well matched for age, sex, diagnosis and operative details. There were more very low anterior resections and hence fewer sutured anastomoses in the 'test' group but this difference was not significant (*Table 1*).

Eighteen (25 per cent) air leaks in the 'test' group were detected at the time of operation and repaired. After surgery there were three (4 per cent) clinical leaks in the 'test' group and ten (14 per cent) in the 'no test' group (Fisher's exact test, $P = 0{\cdot}043$). There was one death following a clinical leak in the 'test' group and two such deaths in the 'no test' group. There were eight (11 per cent) radiological leaks in the 'test' group compared with 20 (29 per cent) in the 'no test' group (Fisher's exact test, $P = 0{\cdot}006$). Of the 18 patients in the 'test' group who had an air leak repaired, there was one clinical and two radiological leaks. Four patients in the 'no test' group did not receive a contrast enema because a clinical leak had already necessitated a further operation. The other nine patients with a clinical leak also had a radiological leak.

The number of clinical leaks for both groups combined was 13 (9 per cent) and radiological leaks alone 19 (13 per cent), giving a total of 32 (22 per cent). The only risk factor that was significantly associated with leakage was the level of the anastomosis (*Table 2*). Nine (28 per cent) leaks (five of them clinical) were associated with double-stapled very low anterior resections which constituted only 21 (15 per cent) of the total number of operations (χ^2 test, $P = 0{\cdot}05$). The leak usually arose from the point where the circular staple line intersected the linear staple line (*Figure 2*). Of the 13 patients with clinical leaks, four developed a pyrexia and lower abdominal tenderness that resolved on antibiotics, three received a transverse defunctioning colostomy (one died), two a laparotomy, lavage and transverse colostomy, and four a laparotomy, lavage and Hartmann's procedure (two died). The overall mortality rate following a clinical leak was 23 per cent. Although there were four radiological leaks in patients with a defunctioning transverse colostomy, none of them had any evidence of a clinical leak.

The limited water-soluble contrast enema on the tenth postoperative day was not without problems. Two patients developed lower abdominal pain and tenderness immediately after the contrast enema, which had demonstrated a radiological leak. One settled on antibiotics but the other required a Hartmann's procedure. Two patients developed a Gram-negative septicaemia following the contrast enema. One had a clinical and radiological leak but the other had no evidence of either. He subsequently developed acute renal failure, which resolved, but died 2 weeks later of a probable myocardial infarction.

Discussion

Many factors have been implicated in the aetiology of anastomotic failure including colonic blood flow, bacterial contamination, anastomotic distraction, drains, the level of the anastomosis and the use of sutures or staples[5]. However, the Large-Bowel Cancer Project, which studied 1466 patients in 27 hospitals, showed no statistically significant difference in the incidence of anastomotic leakage for any of these factors except for the level of the anastomosis[2]. The most important factor appeared to be surgical technique, as the incidence of clinical leaks for 28 surgeons varied from 0·5 per cent to over 30 per cent.

The frequency of anastomotic leakage also depends on how carefully it is sought. In a series of 137 colorectal anastomoses, Goligher *et al.*[6] reported a clinical leak rate of 6·5 per cent, but

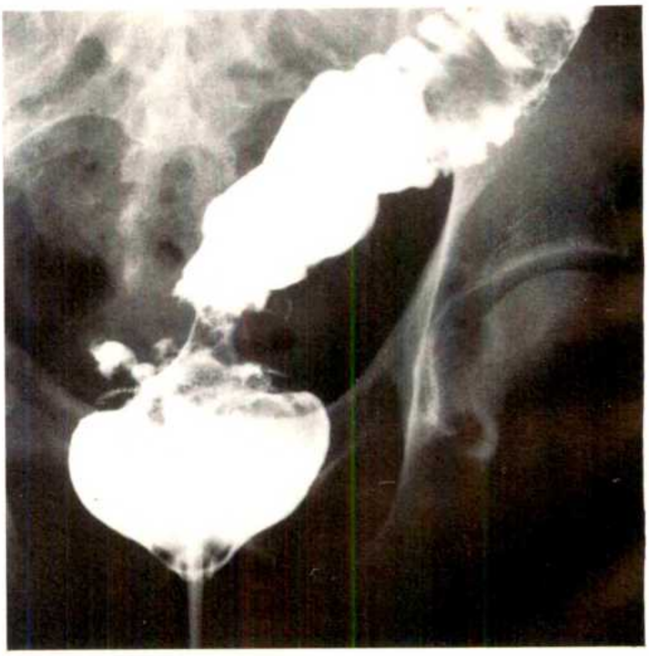

Figure 2 *Water-soluble contrast enema of a double-stapled very low anterior resection. A small leak can clearly be seen arising from the intersection between the linear and circular staple lines*

a further 28·5 per cent were detected radiologically giving a combined leak rate of 35 per cent.

The introduction of anastomosis workshops[7] for the training of surgeons is to be encouraged but there appears to be scope for further improvement. Two small studies have recently suggested that intra-operative testing of colorectal anastomoses might reduce postoperative leakage by permitting the detection and repair of any defects. Gilbert and Trapnell[3] tested 21 anastomoses by rectal distension with saline instilled via a Foley catheter. Five (24 per cent) saline leaks were detected and repaired with no postoperative clinical leaks. Davies *et al.* [4] tested 33 anastomoses by rectal distension with air insufflated via a Foley catheter. Six (18 per cent) air leaks were detected and five repaired. After surgery there were four (12 per cent) clinical leaks and ten (30 per cent) radiological leaks. In the five patients who had an air leak repaired there was only one clinical and one radiological leak.

This randomized controlled trial of 143 colorectal anastomoses confirms the benefit conferred by intraoperative air testing and repair The incidence of clinical and radiological leaks in the 'test' group was one-third that of the 'no test' group, which was statistically significant. Air leaks were detected and repaired in 25 per cent of anastomoses in the 'test' group which probably accounted for this difference. The method used for testing was chosen for practical reasons and hence acceptability by surgeons. A sigmoidoscope inserted into the anal canal is a quick way of insufflating the rectum with air and avoids the risk of a Foley catheter balloon disrupting a low anastomosis. The bubbles from any air leaks can be easily traced and in most cases oversewn. If the leak cannot be repaired then a transverse defunctioning colostomy can be performed.

The intrarectal pressure was not routinely measured as it would have unduly complicated the procedure. Gilbert and Trapnell[3] recommended a pressure of 25 cm saline as being sufficient to detect any leaks but still within physiological limits[8]. However, it is the anastomotic wall tension that is probably more important and this is a difficult entity to measure. Air insufflation with a sigmoidoscope is unlikely to disrupt an anastomosis because, unlike saline, air is compressible and so a rapid rise in pressure with increasing volume does not occur. A Foley catheter balloon can also impact in the anal canal as the pressure increases whereas air tends to vent around a sigmoidoscope The intrarectal pressure was measured in five patients and could not be raised above 35 mmHg due to venting of air. No anastomoses in this study were disrupted by air testing.

The overall clinical leak rate of 9 per cent compares favourably with the findings of another large multicentre study[1] The higher leakage rate for double-stapled very low anterior resections is also in keeping with previous studies which have reported a relationship with the level of the anastomosis[1,2,6]. It was not possible to say whether the low level of the anastomosis or the double-stapled technique was the most significant factor as the two were so closely linked. The high morbidity and mortality following clinical leakage[1] and the higher incidence of radiological leaks[6] were again confirmed. The routine use of a limited water-soluble contrast enema on the tenth postoperative day was not without risk. Previous studies have suggested that its role is primarily as a research tool to define the true anastomotic leak rate[9]. This study confirms that view as two anastomoses were probably disrupted and two patients developed a Gram-negative septicaemia following the procedure.

In summary, intraoperative air testing and repair of colorectal anastomoses is a quick and simple method of permitting the detection and repair of any defects Its use significantly reduces the incidence of postoperative clinical and radiological leaks.

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Malignant left-sided large bowel obstruction managed by subtotal/total colectomy

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Of 60 patients presenting with acute obstructing carcinoma of the left colon, 49 underwent immediate resection either by radical subtotal/total colectomy (31 patients, group I) or by radical segmental resection (18 patients, group II) of whom three had immediate anastomosis after on-table bowel irrigation and 15 had a planned staged procedure. The operative mortality rate was 3 per cent in group I and 11 per cent in group II (not a statistically significant difference). However, substantial differences were found for major morbidity (6 versus *44 per cent in groups I and II respectively;* $P<0{\cdot}01$*) and mean length of hospital stay (17 days in group I* versus *35 days in group II;* $P<0{\cdot}05$*). All three patients who had on-table lavage developed anastomotic leaks which necessitated a second operation to form a stoma. Six patients (19 per cent) in group I required antidiarrhoeal medication in the immediate postoperative period. However, subsequent improvement in stool frequency was noted in all patients. It is concluded that subtotal/total colectomy is an acceptable means of managing patients with obstructing carcinoma of the left colon in that it is associated with a low morbidity and mortality rate and good functional results.*

Keywords: Intestinal obstruction, large bowel cancer, subtotal colectomy

Patients presenting with acute large bowel obstruction secondary to colorectal cancer have both a higher operative mortality rate and a poorer overall survival than those presenting with non-obstructing colonic cancers[1–3]. While 96 per cent of over 200 cases of right-sided large bowel obstruction in the Large Bowel Cancer Project were treated by primary resection, opinion as to the preferred management of obstructing carcinoma of the left colon was divided, with increasing numbers of staged procedures being performed the more distal the site of the tumour[1]. Traditionally, left-sided large bowel obstruction has been managed by a three-stage procedure; initial decompression, resection with anastomosis, and subsequent closure of the stoma. The patient thus undergoes three operations, each with its own associated morbidity and mortality rate.

In 1974 Fielding and Wells[4] suggested that a policy of primary resection might improve survival. This can be accomplished by either resection and anastomosis (with or without a proximal defunctioning stoma), or a staged procedure involving resection and delayed anastomosis (Hartmann's operation). The results of the former policy have not been uniform, but had operative mortality rates ranging from 8 per eent[5] to over 30 per cent[6,7]. A high incidence of major morbidity such as wound dehiscence and anastomotic leaks has also been reported[4,6]. In view of these results and their personal experience, Irvin and Greaney[7] advised against primary resection and immediate anastomosis for obstructing lesions in the left colon.

Although the analysis of 713 patients with large bowel obstruction[1] refuted the survival advantage suggested with a policy of primary resection, it was still favoured by many surgeons and, until the advent of on-table lavage[8], patients having a primary resection were treated in two stages (primary resection and subsequent closure of stoma). The development of the technique of intraoperative colonic lavage allowed the combination of primary resection and immediate anastomosis. Recently a number of uncontrolled series have reported its successful use in left-sided colonic obstruction[9–13].

An alternative strategy, which not only accomplishes primary resection of the tumour but also allows a primary anastomosis, is one of subtotal/total colectomy. Enthusiasm for this approach has been tempered by suggestions that patients suffer from an unacceptable frequency of diarrhoea, a problem which can be troublesome in the elderly. Nevertheless within the last decade this procedure has gained popularity, with an increasing number of favourable reports[14–22].

Over the past 4 years we have used this method with increasing frequency and herein report our experience with this and other policies in the management of obstructing carcinoma of the left colon.

Patients and methods

During the period January 1985 to June 1989, 60 patients presented with obstructing carcinoma of the left colon (at or distal to the splenic flexure). The cases were identified from the emergency operating theatre register and a proforma was used to collect data for each case Forty-nine (82 per cent) patients underwent immediate tumour resection. Eleven (18 per cent) patients were treated by either laparotomy alone (one patient) or by the formation of a defunctioning colostomy. These cases were excluded as no primary tumour resection was performed

Of the 49 patients undergoing immediate resection 31 were treated by either subtotal or total colectomy and primary anastomosis (group I). The other 18 patients formed group II Three of them had on-table lavage and primary anastomosis and 15 had a two-stage procedure of which a Hartmann's operation was the most common.

The site of the tumour was as defined by Aldridge *et al.*[23] . The splenic flexure describes the left third of the transverse colon, the angle and the first part of the descending colon, and the left colon describes the descending colon and the sigmoid

The hospital stay was defined as the total time spent in hospital for the presenting complaint, and if necessary for a subsequent procedure such as closure of colostomy

Morbidity was defined as either major or minor Minor morbidity included urinary tract infection, chest infection and wound infection that needed only minor treatment. Major morbidity included more significant wound infections that needed drainage and packing, anastomotic leaks, abscess formation and cardiorespiratory complications which prolonged hospital stay. Mortality was defined as death occurring in hospital.

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The significance of differences between the groups was assessed by use of Fisher's exact test and the Wilcoxon rank sum test, differences were regarded as significant if the probablity of their having arisen by random sampling error was less than 1 in 20.

Results

The 49 patients comprised 29 men and 20 women (mean age 71, range 50–88 years).

In group I (31 patients) three operative methods were used: ileo-descending colon anastomosis (16 patients, 52 per cent), ileosigmoid anastomosis (10 patients, 32 per cent) and ileorectal anastomosis (five patients, 16 per cent). In no case was a loop ileostomy used to defunction the distal anastomosis. Of the 18 patients in group II, 13 underwent a Hartmann's procedure, one a modified Hartmann's procedure (end colostomy and mucus fistula) and one a Paul–Mikulicz procedure. The final three patients in group II underwent on-table lavage followed by restoration of intestinal continuity without a covering colostomy. All three patients developed clinical evidence of anastomotic dehiscence that necessitated further operation with the formation of a stoma.

The mean age was 73 years (range 50–88 years) in group I and 65 years (range 50–82 years) in group II. Comparison of group I with group II showed no clinical differences for the location of the primary tumour or Dukes' stage (*Table 1*) except that all splenic flexure tumours were treated by subtotal colectomy.

The overall frequency of synchronous tumours was 8 per cent (four patients) At operation only three of these were noted, the histological examination of a subtotal colectomy specimen revealing the fourth, a Dukes' B carcinoma of the caecum. Two of the three patients were treated by subtotal colectomy and the other had undergone a combination of right hemicolectomy and a Hartmann's procedure. In addition, an early metachronous (missed synchronous) tumour was detected in a further patient 3 years after her Hartmann's procedure had been performed for a Dukes' B carcinoma of the sigmoid.

There were three hospital deaths in the study group (overall mortality rate 6 per cent), one patient (3 per cent) died in group I and two (11 per cent) in group II (n.s., *Table 2* for patient details).

Major morbidity was seen in two patients (6 per cent) in group I and in eight patients (44 per cent) in group II This difference achieved statistical significance (Fisher's exact probability test, $P=0{\cdot}0053$). Of the two patients in group I who suffered major postoperative complications one was the only case in the series with faeculent peritonitis. This was caused by the perforation of a synchronous tumour, from which the patient developed numerous intra-abdominal abscesses. The other was a wound infection in an 82-year-old woman with a Dukes' C tumour of the splenic flexure infiltrating the anterior abdominal wall. No patient in this group developed evidence of an anastomotic leak Two patients in group II developed a pelvic abscess. In both cases this was a direct consequence of the procedure performed. In one, the abscess was a result of rectal stump dehiscence and in the other it was secondary to retraction of the distal limb of a double barrelled colostomy. In addition to these cases there were two wound infections and one pericolostomy abscess. All three patients undergoing primary resection and anastomosis after lavage developed evidence of a clinical leak and pelvic sepsis. Two were treated by laparotomy, peritoneal lavage and the formation of a proximal stoma and one was converted to a Hartmann's procedure. Minor morbidity was seen in 16 per cent of patients in group I: two chest infections, two urinary tract infections and one wound infection (*Table 3*).

The median hospital stay for the patients in group I was 15 days (range 8–40 days). This was significantly different (Wilcoxon's rank sum, unpaired data (two tail), $P<0{\cdot}05$) from that of the patients in group II whose median stay was 32 days (range 12–88 days).

The majority of the operations in both groups were performed by surgeons in training (*Table 3*). The in-hospital mortality rate was not significantly different between grades of surgeon (one death each). Likewise, the morbidity that accompanied the procedure was not dependent on the seniority of the surgeon (consultant 25 per cent, trainee 20 per cent).

In the immediate postoperative period, six patients (19 per cent) in group I, two of whom had had ileorectal anastomoses, complained of diarrhoea. However, in none was this refractory to antidiarrhoeal medication or associated with faecal incontinence.

Follow-up ranged from 6 to 54 months, with a mean of 20 months in group I compared with a mean of 15 months in

Table 1 *Location and Dukes' stage of obstructing tumour*

	Group I $n=31$	Group II $n=18$
Site		
Splenic flexure	16	0
Left colon	10	13
Rectosigmoid	5	5
Dukes' stage		
A	1 (3)	0 (0)
B	10 (32)	4 (22)
C	12 (39)	8 (44)
'D'	8 (26)	6 (33)

Values in parenthese are percentages

Table 3 *Mortality rate, morbidity and surgical seniority of operator*

	Group I $n=31$	Group II $n=18$
Mortality	1 (3)	2 (11)
Morbidity		
Minor	5 (16)	1 (6)
Major	2 (6)	8 (44)
Grade of surgeon		
Consultant	7 (22)	5 (28)
Senior Registrar	8 (26)	5 (28)
Registrar	16 (52)	8 (44)

Values in parentheses are percentages

Table 2 *Clinical details of patients who died in hospital*

Age	Sex	Site of tumour	Dukes' stage	Procedure performed	Time (days)	Cause of death	Comment
74	M	Left colon	'D'	Paul–Mikulicz procedure	51	Septicaemia, Pelvic abscess	Retraction of distal limb
82	F	Left colon	C	Hartmann's procedure	62	Septicaemia, Pelvic abscess	Dehiscence of rectal stump, Second operation
86	M	Splenic flexure	C	Subtotal colectomy	4	Gangrene, right leg	Unsuccessful embolectomy, Anastomosis intact at post mortem

group II. Of patients in group II, 56 per cent died with their colostomy *in situ* over a period ranging from 5 to 15 months. Of the remaining eight patients, two have had their colostomies closed, four are awaiting closure (although two had not been closed by 1 year), one has had an attempt at reversal which failed and one has been lost to follow-up. Of those treated by subtotal/total colectomy, 11 patients (35 per cent) died over a period ranging from 4 to 36 months. The pattern of Dukes' staging of these deceased patients was similar in both groups (group I: B, 18 per cent; C, 36 per cent; D, 45 per cent *versus* group II: B, 10 per cent; C, 40 per cent, D, 50 per cent).

Of the survivors in group I ($n=20$), 17 patients (85 per cent) were interviewed with respect to their stool frequency and the need to use antidiarrhoeal drugs. Although drugs to control diarrhoea were still occasionally used when necessary, no patient relied on their regular use and all had decreased stool frequency when compared with the immediate postoperative period (*Table 4*)

Discussion

The idea of removing the entire dilated colon proximal to an obstructing tumour is not a new one. In 1914 Lane[24] suggested this option, but there were no series of patients reported until 1965 when Hughes and Cuthbertson described their experience with 12 patients[25]. They had one postoperative death and recommended the approach in selected patients. In 1981 Klatt *et al.*[14] reported their results with five patients whose tumours were more distally placed than those in Hughes and Cuthbertson's series. There was no mortality or significant major morbidity and although the patients were relatively young (mean age 55 years), the average length of hospital stay was only 8 days.

Our overall mortality rate (6 per cent) compares favourably with that reported by Phillips *et al.*[1] for either primary resection (19 per cent) or a staged procedure (22 per cent). Though the in-hospital mortality rate appears to be improved for subtotal/total colectomy (3 per cent) *versus* those treated by other methods (11 per cent), this difference did not reach statistical significance. However, the causes of death in these patients do have different explanations. The two deaths in group I were a direct consequence of the procedures performed, with both patients dying of septicaemia, but the cause of death in the patient in group I was unrelated, namely a peripheral embolus in an elderly patient with pre-existing atrial fibrillation. The technical complications responsible for the two deaths in group I might have been avoided if the rectal stump had been washed out before closure. Moreover, even though the formation of a mucus fistula may be preferable, if the mucus fistula creates tension the rectal stump should be irrigated, closed and sutured to the sacral promontory.

Table 4 *Mean daily stool frequency at various intervals after subtotal/total colectomy*

Site of obstructing tumour	On discharge	At 2 months	At 6 months or more
Splenic flexure	2 (1–4)	2 (1–3)	1 (1–2)
Left colon	3 (2–5)	2 (2–4)	2 (1–3)
Rectosigmoid	3 (2–5)	3 (2–4)	3 (2–4)

Values in parentheses are ranges

Obstruction managed by a staged procedure is not uncommonly complicated by a significant degree of morbidity[1,6,26] and certainly, in this study, major morbidity was more common in group II ($P<0·01$). Although minor morbidity appears over twice as common in group I, most of the patients with major morbidity in group II also experienced less serious complications which are not recorded separately.

Within the last 10 years a number of series have reported the use of subtotal/total colectomy with encouraging results[14–22] (*Table 5*). The overall mortality rates in these series, which comprise almost 200 patients, with an average age of 67 years, is only 8 per cent. This compares favourably with mortality rates of 16–38 per cent in patients of similar age presenting with large bowel cancer[27–29]. Two of our deaths (11 per cent in group II) were caused by technical complications, and although this rate is not high such complications are not an uncommon problem after staged procedures[26,29]. In our series there were no anastomotic leaks associated with subtotal/total colectomy group and the death in this group was due to an unrelated thromboembolic complication. Of all the deaths in the collected series referred to above[14–22], the majority of known causes were cardiorespiratory complications. Moreover, anastomotic leaks were uncommon (overall incidence 3 per cent), accounting for the generally low incidence of major morbidity (mean 8 per cent). These favourable figures, and the observation of a generally smooth convalescence, have led some authors to suggest that this form of treatment should be used in most[16,20,22] and certainly in selected[14,18,19] patients with obstructing carcinoma of the left colon.

Four of the patients (8 per cent) in this series had synchronous tumours, but only three of these were detected at operation. Removal of the entire proximal colonic mucosa eliminates the problem of the 'missed' synchronous tumour and avoids the development of a metachronous lesion in that segment. Synchronous neoplasms (adenomas and carcinomas) are present in 58 per cent of patients with occluding tumours[30] and, of these, 48 per cent have neoplasms proximal to the

Table 5 *Data from previous reported series of subtotal colectomy*

	n	Mean (years)	Mortality rate (%)	Morbidity (%) Minor	Morbidity (%) Major	Mean hospital stay (days)
Hughes and Cuthbertson[25]	12	65	8	n.s.	8	n.s.
Klatt *et al.*[14]	5	55	0	40	0	8
Glass *et al.*[15]	7	71	14	n.s.	14	21
Deutsch *et al.*[16]	14	72	7	21	14	18
Hughes *et al.*[18]	52	n.s.	11·5	n.s.	n.s.	n.s.
Morgan *et al.*[17]	16	69	12·5	n.s.	6	n.s.
Halevy *et al.*[20]	8	67	0	37	12·5	n.s.
Feng *et al.*[19]	9	62	11	n.s.	n.s.	17
Wilson and Collock[21]	18	70	11	44	0	15
Halevy *et al.*[22]	22	67	4·5	23	13	26
Present series	31	73	3	16	6	17

n.s., not stated. An acceptable mortality, morbidity and hospital stay is seen despite an elderly population obstructing tumour Coupled with the fact that, with increasing age, polyps are more commonly found in the right colon[31], it is reasonable to suspect that the metachronous carcinoma in our patient developed in such an adenoma, presumably impalpable in the dilated caecum at the first operation. This 'early' metachronous carcinoma (missed synchronous tumour) occurring within 3 years might not have been missed if a policy of 'thorough investigation of the whole large bowel' had been deployed in the operative or early postoperative period[32].

A further benefit of subtotal colectomy is a reduced hospital stay, which has both social and economic implications. The mean hospital stay in those patients in our series was 17 days This was half that of our group II patients ($P<0.05$) and is comparable with that of Phillips *et al.*[1] where the mean stay after staged resection was 40 days

The outcome after surgery for acute large bowel obstruction has been said to depend on the seniority of the surgeon. Although both Goligher[33] and Hughes[18] support the use of subtotal colectomy, they both describe it as a demanding procedure which should be performed only by well trained surgeons. Phillips *et al.*[1] quoted a hospital mortality rate of 24 per cent when surgeons in training performed primary resection in the presence of obstruction This was compared with a figure of 13 per cent when the operation was performed by a consultant. However, they added that patient selection probably accounted for this difference as both registrars and consultants had similar mortality rates when performing elective colorectal surgery. In our series surgeons in training performed just over three-quarters of the operations with mortality and morbidity rates that were no worse than in operations performed by consultants, a finding in agreement with that of Mealy *et al*[34] In our experience, surgeons in training have found anastomosis after on-table lavage a more difficult procedure than subtotal/total colectomy, but it is not possible to draw conclusions from three cases

One of the criticisms of subtotal colectomy is that it results in the frequent passage of liquid stools. This is certainly the case in the immediate postoperative period, especially after ileorectal anastomoses where two (40 per cent) of five of our patients needed antidiarrhoeal medication. However, the situation in these patients, and in the group overall, improved after 3–4 months and we did not find any patient using drugs on a regular basis Moreover, we did not record any complaint of nocturnal urgency (excluding the early postoperative period) or of incontinence Similar observations have also been made in previous series[14–17,19,21,22]

Clearly the avoidance of a colostomy, particularly in an elderly population, is desirable Though 56 per cent of patients in group II died with their colostomy *in situ*, the intention had been to close it in half of them. If the eight patients with Dukes' 'D' tumours in group I had undergone staged procedures, intestinal continuity would undoubtedly not have been restored. This would have left 37 per cent of our patients to die with their colostomies *in situ*, a high but nevertheless well recognized proportion[26,34] If a colostomy can be avoided in a palliative procedure, without increasing the immediate mortality, this is obviously preferable. If intestinal continuity is not restored at the initial procedure, the likelihood that it will be restored decreases with time, as patients die or are later considered too frail and unfit to complete their surgical treatment. In patients with residual or metastatic disease the avoidance of a colostomy is probably more important than survival, but many undergoing staged procedures for advanced disease are unfortunately left with a permanent colostomy[1,26,29,34]

We were unable to draw any firm conclusions on the long-term survival of the patients undergoing subtotal/total colectomy. However, those dying in group I did so over a longer period when compared with those in group II with a similar Dukes' stage Previous reports are also unhelpful when addressing the question of whether this form of treatment improves long-term survival Obstructing carcinomas are associated with a poor 5 year survival rate[1–3], and this may be due to the increase in local recurrence seen in these patients even after curative resection[3]. The prognosis may be improved by surgical excision which includes a wider area of lymphatic drainage[23] For splenic flexure carcinomas this is accomplished by extended right hemicolectomy. The scope of this procedure can be further extended to encompass an obstructing carcinoma of the left side by performing a subtotal or total colectomy with ileosigmoid or ileorectal anastomosis.

There is a move towards definitive surgery for left-sided large bowel obstruction (primary resection, on-table colonic lavage, subtotal/total colectomy), but long-term prospective controlled trials, possibly randomized, are required to evaluate the benefits of these techniques. Our results support the suggestion by others that subtotal/total colectomy is the treatment of choice for the majority of patients with malignant left-sided large bowel obstruction.

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Complications of diverticular disease and non-steroidal anti-inflammatory drugs: a prospective study

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Previous retrospective studies have suggested an association between consumption of non-steroidal anti-inflammatory drugs (NSAIDs) and the complications of diverticular disease. Ninety-two patients were entered into a prospective study of the complications of diverticular disease over a 3 year period; 31 were taking NSAIDs, compared with only four age- and sex-matched controls from a representative general practice ($P<0{\cdot}001$)*. A second control group comprised 306 patients with cancer of the colon in whom NSAID consumption was again significantly lower than in patients with diverticular disease (22 of 306* versus *31 of 92,* $P<0{\cdot}001$)*. Of the 31 patients taking NSAIDs, 19 presented with a perforation or peritonitis. By contrast, only eight of the 61 patients not taking NSAIDs had such complications* ($P<0{\cdot}001$)*. Eleven patients presented with bleeding of whom five were taking NSAIDs and six were not. Patients admitted with complications of diverticular disease have a high incidence of NSAID intake, and it appears that NSAID consumption is associated with a more severe form of the disease.*

Keywords: Diverticular disease, complications, non-steroidal anti-inflammatory drugs

Diverticular disease is common in Western society but its complications are relatively uncommon[1]. However, the number of operations performed each year for complications of diverticular disease[2] in Lothian over the period 1980–1988 has increased from 47 to 70. A previous study suggested an association between the consumption of non-steroidal anti-inflammatory drugs (NSAIDs) and bleeding or perforation of the small and large bowel[3]. The number of prescriptions dispensed for NSAIDs in the UK has increased from 7·6 million in 1967 to 22 million in 1985[4]; this increase in prescribing habits is most marked in women over 65 years of age.

Previous studies suggesting an association between the complications of diverticular disease and NSAIDs[3,5] were retrospective and thus the accuracy of a history of NSAID consumption and its recording in the case record remains suspect. We have performed a prospective study of all patients admitted to our surgical unit over a 3 year period in whom a final diagnosis of diverticular disease was made. By comparing NSAID consumption in patients with both uncomplicated and complicated disease with appropriate controls, we sought to establish whether a relationship existed between NSAID consumption and the development of a complication of diverticular disease.

Patients and methods

All patients admitted to the Western General Hospital, Edinburgh with abdominal pain were studied prospectively between July 1986 and July 1989. All patients in whom a diagnosis of diverticular disease was considered but who did not come to operation had a colonoscopy and/or barium enema performed. All patients in whom a final diagnosis of diverticular disease was confirmed by these examinations were included in the study. Complications of diverticular disease were considered under the headings localized diverticulitis, generalized peritonitis (including perforation) and bleeding. Localized diverticulitis included patients in whom a diagnosis of peridiverticulitis or pericolic abscess was made on the basis of clinical signs in the abdomen supported by a leucocytosis. The diagnosis of perforated diverticular disease with free peritonitis was confirmed by laparotomy in each case. Bleeding diverticular disease was diagnosed on the basis of haemorrhage thought to be from the lower gastrointestinal tract with subsequent confirmation of diverticular disease by colonoscopy and barium enema.

Information about drugs being taken by the patients was specifically sought on admission by detailed interview. The indication for NSAIDs together with frequency and duration of intake was recorded in addition to any previous history of symptomatic diverticular disease.

For each patient with diverticular disease an age- and sex-matched control, not known to have diverticular disease, was selected from the age/sex register of a large general practice located in the centre of the hospital catchment area. Current NSAID prescription in these control patients was recorded. A second control group comprised 306 colorectal cancer patients whose clinical details (including NSAID consumption) are recorded as part of a prospective audit. They had an F:M ratio of 1:1 and a median age of 68 years (range 44–85 years). These patients were studied to control for possible bias in NSAID intake caused by the presence of lower bowel symptoms. Statistical analysis between groups was by χ^2 test with Yates' correction when groups contained less than ten subjects.

Results

Ninety-two patients (57 women and 35 men, F:M ratio 1·6:1) who fulfilled the diagnostic criteria for complications of diverticular disease were recruited in the study period. The median age was 70·9 years with a range of 35–93 years. At the time of admission, 31 patients (34 per cent) were taking NSAIDs. The indications for NSAID in these 31 patients were osteoarthritis in 32 per cent, rheumatoid disease in 29 per cent, back pain in 16 per cent and other indications in 23 per cent. Patients took 13 different types of NSAID; in 29 cases these were at the dose prescribed by a medical practitioner, while two patients were self-medicating with ibuprofen. The duration of NSAID intake before admission ranged from 4 weeks to 5 years.

Only seven of the 31 patients taking NSAIDs presented with diverticulitis, but 47 of the 61 who were not taking NSAIDs presented in this way ($P<0{\cdot}001$). By contrast, 19 of the 31 patients taking NSAIDs presented with perforation compared with only eight out of 61 not taking NSAIDs ($P=0{\cdot}001$). Of the 11 patients presenting with bleeding, five were taking

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NSAIDs and six were not This difference was not statistically significant. Five patients in the NSAID group had a previous history of diverticular disease, as did 15 in the non-NSAID group. There was no significant difference in age between the NSAID group (median 75 years, range 35–89 years) and the non-NSAID patients (median 67 years, range 43–94 years)

The possibility exists that NSAID consumption might merely be an indicator of rheumatoid disease or corticosteroid consumption, conditions which themselves might be associated with complications of diverticular disease. Ten patients in the NSAID group had rheumatoid disease while none of the 61 patients not taking NSAIDs had this diagnosis. In the NSAID group six patients, all with rheumatoid disease, were on corticosteroid treatment while four in the non-NSAID group were taking steroids. Even with exclusion of these 14 patients from the analysis, patients taking NSAIDs remain significantly ($P<0·001$) more likely to present with perforation (12 of 21) than those not taking NSAIDs (7 of 57). Of the 21 patients taking NSAIDs, four presented with local signs compared with 44 of 57 not taking NSAIDs ($P<0\ 001$) As before, there was no significant difference in NSAID consumption in patients presenting with bleeding.

NSAID consumption was compared between 92 patients presenting with diverticular disease and age- and sex-matched controls. Of the 92 patients with diverticular disease, 31 (34 per cent) were taking NSAIDs By contrast only four (4 per cent) of the 92 age- and sex-matched controls were taking NSAIDs ($P<0·001$). Of the 306 disease-positive controls, 22 (7·2 per cent) were taking NSAIDs at the time of admission to hospital, which is significantly fewer than the patients with diverticular disease ($P<0·001$). There was no significant difference in the NSAID intake of the two control groups.

Discussion

This is the first prospective study of the association between NSAID consumption and complications of diverticular disease. Fewer patients with localized diverticulitis were taking NSAIDs at the time of presentation, a finding which gives even greater emphasis to the significant excess of NSAID consumption in patients presenting with perforation This is the strongest evidence to date for a relationship between NSAID consumption and perforation of diverticular disease. The association between NSAID consumption and upper gastrointestinal bleeding has been the subject of much debate[6]. Unlike Langman *et al*[3] we found no association with bleeding diverticular disease, possibly because our study included relatively few of these patients but more probably because their study included patients with haemorrhage from other sites within the intestine

The proportion of age- and sex-matched control patients taking NSAIDs in our study was 4 per cent compared with 7·2 per cent in our large bowel cancer control group and 9·3 per cent in Langman's series of hospital controls. Langman *et al.*[3] suggest that some 10 per cent of the population over 60 years of age have recorded NSAID intake. The proportion may be less in our series because 19 of the patients (20 per cent) were less than 60 years of age. All of the age- and sex-matched control patients recorded as taking NSAIDs in our study were over 60

NSAID consumption as judged by the number of prescriptions written is increasing[4], as are the number of operations for perforated diverticular disease in our area[2]. This study provides further evidence of a causal relationship between these two observations.

Possible mechanisms for NSAID-associated perforation of diverticular disease may be the direct anti-inflammatory action of these agents on the bowel itself or their inhibitory effects on leucocyte function[7,8] with a resultant failure of the inflammatory response to localize the disease process

Our study, in common with previous retrospective studies[3,5], has considered only prescribed NSAIDs Ibuprofen is now available without prescription but only two of our patients were taking this preparation. We have no information about possible ibuprofen consumption in the general practice controls.

NSAIDs produce relief from joint pain and are increasingly prescribed in patients over 60 years of age, about one-third of whom may have diverticular disease The balance of pain relief against inducing perforation in diverticular disease falls heavily in favour of pain relief. The minority (<25 per cent) of patients in this series were known to have diverticular disease at the time an NSAID was prescribed. Given the frequency of joint pain and the relative infrequency of perforated diverticular disease in Western society, it would be inappropriate to withhold NSAIDs even in patients known to have diverticular disease Nevertheless, the clear association of perforated diverticular disease with NSAIDs should be recognized by all doctors prescribing these drugs.

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Intraoperative testing of colorectal anastomosis can be misleading

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Anastomotic dehiscence is a major cause of mortality and morbidity following colorectal surgery[1]. It has been suggested that intraoperative air or saline testing of anastomoses to the rectum might reduce the risk of postoperative leakage by highlighting suture line defects at operation, which can then be oversewn[2,3]. This study reports the use of this test in a series of patients in whom a double stapling technique was used for colorectal anastomosis.

Patients and methods

Eighty-two patients, 39 men, median age 67 years, underwent rectal or rectosigmoid excision and colorectal anastomosis. In each patient linear (TA55®, US Surgical Corporation, Norwalk, Connecticut, USA) and circular (EEA®, 28 mm or 30 mm, US Surgical Corporation) instruments were used to create a double-stapled anastomosis using the technique first described by Knight and Griffen[4] The level of the anastomosis was defined as low when stapling was to the completely extraperitoneal rectum, as described by Goligher *et al.*[5] On completion of stapling the colon was occluded by a soft clamp and anastomotic integrity tested by filling the pelvis with saline and insufflating air into the rectum with a bladder syringe. Defects were recognized by the escape of air bubbles and were closed by suture before retesting A defunctioning stoma was used if judged clinically appropriate by the surgeon at the time of operation Every patient with any of the following underwent a Gastrografin® enema (Schering Health Care Ltd., Burgess Hill, UK) prolonged ileus, unexplained fever, tenderness and distension or rectal discharge. The diagnosis of anastomotic leakage was based on the result of radiography, however minor the defect Record was made of the level of anastomosis, air leakage, tissue ring integrity and postoperative anastomotic leakage. Statistical analysis was by χ^2 test with Yates' correction for small numbers

Results

The results of air testing and subsequent clinical outcome are shown in *Table 1*. The overall clinical leakage rate was 10 per cent (8 of 82). Six of these were minor and were managed without further surgery but two were major and required a further laparotomy and loop ileostomy. Leakage was not related to Dukes' staging of cancer or to emergency operation (five cases) Inspection of tissue doughnuts after stapling showed incomplete rings on seven occasions. Orientation of the EEA instrument enabled these potential leakage sites to be reinforced by suture, and all proved airtight on testing. None of this group subsequently leaked. All eight leaks occurred in anastomoses which had physically intact tissue rings.

Discussion

Anastomotic defects were demonstrated at operation in 6 per cent of colorectal anastomoses using an intraoperative air test. Suture of the defect was followed by postoperative leakage in one patient and four had an uncomplicated recovery It is likely, but not proven, that air testing spared these four patients the sequelae of a postoperative anastomotic leak. This conclusion agrees with that of Davies *et al.*[2], who used an air test in 33 patients undergoing a variety of colorectal anastomoses with six (18 per cent) air leaks and four (12 per cent) clinical leaks. Gilbert and Trapnell[3] used a saline test and recommended that a distending pressure of 25 cm of saline be used to test the anastomosis. They observed five (24 per cent) saline leaks in 21 patients studied with a postoperative leak in only one case. They do not, however, give the number of low anastomoses and also some were described as colocolonic. Our results also show that the intraoperative test may be misleading. All eight leaks in the current series were airtight at intraoperative testing, all had intact tissue rings on completion of stapling and all anastomoses were to the extraperitoneal rectum. All anastomoses in this series were carried out by the technique of double stapling and in their original description Knight and Griffen[4] comment on the considerable reassurance they gained from checking the integrity of their staple lines with saline irrigation before abdominal closure We anticipated that the construction of a confirmed airtight anastomosis would result in a low postoperative leakage rate and the results are, therefore, disappointing.

Table 1 *Level of anastomosis and sequelae of air leak*

Anastomotic level	*n*	Stoma	Postoperative leak†
High ($n=37$)			
Air leak	1	0	0
No leak	36	2	0
Low ($n=45$)			
Air leak	4	3	1
No leak	41	8	7*

* Two of this group had a defunctioning stoma at the original operation.
† Postoperative leak rate significantly higher after low anastomosis (8 of 45 compared with zero of 37), $\chi^2=5\ 41$, $P<0\ 25$)

Our results confirm that for the high anterior resection a double-stapled anastomosis is safe. However, a leakage rate of 18 per cent (8 of 45) for low anterior resection was not predicted on the basis of intraoperative air testing, which in each case showed airtight staple lines We conclude that intraoperative anastomotic testing, although not of proven value, seems logical as 6 per cent of our stapled anastomoses required suture reinforcement A satisfactory intraoperative air test, however, will not guarantee uncomplicated healing of the low anastomosis. Leakage in this group must be the result of factors other than the construction of structurally sound staple lines.

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Blood transfusion and recurrence of colorectal cancer: the role of platelet derived growth factors

Efforts to explain the possible effects of blood transfusion on the recurrence of colorectal cancer have been based entirely on the immunosuppressive effects of blood transfusion. However, the relationship between solid tumour development and the immune system is inconclusive. We have investigated an alternative mechanism involving the potential role of growth factors in this phenomenon. Using a human fibroblast: [^{125}I]deoxyuridine uptake mitogenesis assay, the relative amounts of growth factor in the plasma of stored blood were measured. There was a progressive increase in mitogenesis from day 0 (n = 6) to day 28 (n = 6; $P < 0.001$, Mann–Whitney U test). The effect of growth factors on the development of liver and intraperitoneal metastases was studied in Hooded Lister rats. Following an intraportal injection of 10^5 MC28 tumour cells, the experimental group (n = 25) received 2 ml of syngeneic serum intravenously for 4 days. Likewise, colonic anastomoses were performed on omentectomized rats and the peritoneal cavity seeded with 10^3 cells. The experimental groups (n = 20) received either 2 ml serum intravenously repeatedly or 3 ml serum intraperitoneally (n = 19). There was no significant increase in liver metastases or peritoneal disease following intravenous infusion of serum but serum delivered intraperitoneally resulted in a significant increase in tumour from 22 per cent in the controls to 89 per cent in the study group ($P < 0.01$). Growth factors released from platelets following blood loss into the peritoneal cavity may be important in enhancing local recurrence of colorectal cancer.

Keywords: Blood transfusion, cancer recurrence, growth factors, experimental tumour

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Perioperative blood transfusion has been associated with an increased tumour recurrence rate in a wide range of cancers. Attention has focused on recurrence after surgery for colorectal cancer. Recently, several large retrospective studies have shown a significant survival advantage for non-transfused patients even after allowing for other prognostic variables[1,2]. Immunological mechanisms have been proposed to account for this phenomenon following the observation that renal allografts survive longer in patients who have previously received a blood transfusion[3]. Experimental data from laboratory animals confirm the association between allogeneic blood transfusion, immunosuppression and increased tumour growth[4]. However, while it is accepted that blood transfusion alters immune function, these studies do not adequately explain the effect for spontaneous tumours which have little or no immunological activity[5]; or a reduction in antitumour mechanisms occurring as a result of per- or postoperative blood transfusion

It is our contention that growth factors, derived from degranulating platelets, present in the plasma fraction of stored blood or released during haemorrhage may be influencing the survival of tumour cells disseminated during surgery either intravascularly or intraperitoneally

In this study we have investigated the plasma fraction of blood obtained for transfusion with regard to the concentration of mitogens (growth factors) present on donation and on storage We also describe an experimental model to investigate the effect of infusing 'mitogen-rich' serum on tumour growth, both with regard to liver metastases and peritoneal recurrence.

Materials and methods

Investigation of the level of growth factors in stored blood

Six volunteer donors were bled by the Wessex Blood Transfusion Centre into standard, whole blood collection packs containing 63 ml CPDA-1 anticoagulant and stored at 4°C Aliquots of 40 ml were removed from each pack via the sample port, under strict aseptic conditions, on days 0, 3, 7, 14 and 28 of storage. The plasma fraction was separated and prepared for assessment of growth factor activity as described below. Six units of outdated blood packs (i.e. over 35 days old) were also obtained from the transfusion centre and the activity of the plasma used for comparison.

In order to compare overall activity of the stored blood plasma with the maximal levels obtainable, six volunteer donors were bled and whole-blood serum prepared.

Preparation of blood samples for assay

Blood for plasma preparation was taken into 20 ml universal containers and centrifuged at 4°C for 30 min at 800*g* The plasma supernatant was removed and transferred to high-speed centrifuge tubes and spun at 15 000*g* for 30 min at 4°C The resultant particle-free plasma was then transferred to fresh siliconized tubes and immersed in a 56°C water bath for 30 min. A copious fibrinogen precipitate formed which was removed by centrifugation at 800*g* for 30 min at 4°C The heat-inactivated plasma-derived serum thus prepared did not clot.

In order to equilibrate pH and electrolytes and to remove possible artefacts owing to the presence of the anticoagulant solution, each sample was dialysed (through an 1800D exclusion membrane, Sigma Chemical Company, Poole, UK, Cat No 7242) against complete phosphate buffered saline (PBS), pH 7 2, for 18 h at 4°C

Blood for inactivated serum was clotted at 37°C in fresh glass tubes for 40 min The whole blood-derived serum was then separated by centrifuging at 800*g* for 30 min and the supernatants prepared as described above

Samples were then filter sterilized through a 0·22 μm filter and stored at −20°C until assayed.

Mitogenic assay

The mitogenic activity of the processed samples was determined as follows. Human fibroblasts, grown from explants of infant preputial tissue, of low passage, were cultured on 96–well microtitre plates (Nunc) in Dulbecco's Modified Eagles Medium (DMEM) with 10 per cent fetal calf serum (FCS) and penicillin until confluent. The medium was then changed to DMEM with 1 per cent FCS for 48 h before use. Test samples in DMEM (with 25 mM Hepes buffer, insulin, transferrin and 1 per cent bovine serum albumin) were added to each well and the DNA synthesis was measured by [^{125}I]deoxyuridine incorporation into trichloroacetic acid precipitable material.

Each sample was assayed in duplicate, and repeated on a separate assay run and the average uptake in counts/min taken. Results are expressed as a percentage increase in uptake relative to baseline levels achieved by serum-free medium (relative mitogenic activity, RMA per cent)

The effect of 'mitogen-rich' plasma on tumour growth

Animals Syngeneic Hooded Lister rats (male and female, weighing 150–200 g) of the Chester Beatty Institute, maintained as an inbred line in Southampton, were used.

Tumour The MC28 tumour, syngeneic for the Hooded Lister rat, was maintained by subcutaneous passage every 14 days. Only tumours of low passage number (i.e between two and eight passages) were used This particular tumour has been extensively used in the department and has similar seeding characteristics to other experimental tumours[6,7]. It serves well in that single cell suspensions of tumour cells, with high viability, are easily produced.

Preparation of tumour cell suspensions The excised tumour was mechanically disaggregated in Hanks' balanced salt solution (HBSS) A single cell suspension was obtained by incubating the tumour at room temperature on a slowly rotating magnetic stirrer with a protease/DNAase mixture (0 5 mg/ml Sigma no. P5647, 0 005 mg/ml Sigma no D4638) for 30 min Large, undigested fragments were allowed to settle and the cell-rich supernatant was washed and spun for 5 min at 300*g*, three times in HBSS. After the final spin the cell plug was resuspended in DMEM with 10 per cent FCS and penicillin and streptomycin, placed in cell culture flasks and viable cells allowed to adhere over 4–6 h. The cells were then removed using trypsin EDTA (ethylenediaminetetra-acetic acid), rewashed and resuspended in HBSS. Cell counts and viability were determined by Trypan blue dye exclusion. Various concentrations of tumour cells were then prepared by serial dilution of the original suspension in HBSS

Preparation of rat blood samples for infusion. Syngeneic whole blood was obtained from ex-breeder rats, under ether anaesthesia, via direct intracardiac puncture using an 18 Fr needle All animals bled were killed

Due to technical difficulties associated with storing rat blood for more than a few days (red cell aggregation and degradation in spite of red cell preservative) which resulted in approximately 40 per cent of the animals dying following administration, the infusion simulating 'mitogen-rich' plasma in these studies was fresh syngeneic serum (heat-inactivated)

Whole blood was collected as described into plain syringes and decanted into glass containers and allowed to clot for 1 h The specimen was then spun for 30 min at 800*g* and the supernatants saved Supernatants from several animals were pooled and the whole heated in a water bath for 30 min at 56°C.

Investigation into the effect of serum on the growth of liver metastases

Intraportal injections of tumour cells The rats were anaesthetized using ether A midline laparotomy incision was performed and the intestines delivered and laid out over a moist, gauze swab so that the mesenteric vessels were easily seen Using a 24 Fr needle 0 2 ml of tumour cell suspension, containing 10^5 tumour cells in HBSS, was injected into a tributary of the superior mesenteric vein, care being taken to minimize the trauma at this site. Haemostasis was by gentle compression The intestines were returned to the abdominal cavity and the wound closed with two layers of 2/0 silk sutures.

Experimental groups. Animals were divided into two groups; the effect of serum on the development of liver metastases was compared with PBS

Control group ($n=25$) Following wound closure and before recovery, each animal received 2 ml PBS via a lateral tail vein and on 3 successive postoperative days.

Study group ($n=25$): Following wound closure and before recovery, each animal received 2 ml serum via a lateral tail vein and on 3 successive postoperative days

All animals were allowed to recover and a post-mortem was performed 14 days later at a time when liver metastases were easily discernible The livers were removed and sectioned and the number and size of the metastases recorded.

Investigation into the effect of serum on the growth of intraperitoneal tumour

Intraperitoneal tumour cell injections We have previously demonstrated that removal of the greater omentum of the rat 2–3 weeks before tumour inoculation renders the peritoneal cavity refractory to tumour growth at a tumour cell inoculum of 10^3 cells in 1 ml HBSS[8]. The incidence of tumour formation was reduced from 85 per cent of animals to 29 per cent Omentectomy involves removing as much of the omental tissue as possible from the splenic hilum, the greater curve of the stomach (removing the epiploic arcade) and from the retrogastric extension of the omental leaf Haemostasis is by clip-crush and the animals allowed to recover

Under ether anaesthesia, a midline laparotomy incision was made and a colonic anastomosis fashioned using a single layer of interrupted 6/0 silk sutures After completion of the anastomosis a tumour cell suspension of 10^3 cells in 1 ml HBSS was seeded over the anastomosis in the left paracolic gutter The laparotomy wound was closed with two layers of 2/0 silk sutures

Experimental groups. Animals were divided into four groups; two control groups received saline (PBS) and two study groups received serum.

Control groups Group 1 ($n=15$) received 2 ml PBS intravenously via the lateral tail vein after wound closure and before recovery from anaesthesia. Group 2 ($n=18$) received 3 ml PBS delivered into the peritoneal cavity after the tumour inoculum and before wound closure.

Study groups: Group 1 ($n=20$) received 2 ml serum intravenously via the lateral tail vein as in the control group and in order to maximize any possible effect received a further 2 ml on the next 3 days after tumour inoculation. Group 2 ($n=19$) received a single dose of 3 ml serum intraperitoneally after the tumour inoculum and before wound closure

The animals were allowed to recover and post-mortem examination was performed 18 days later The number of animals in which there had been successful intraperitoneal tumour 'take' was recorded with special reference to the areas of surgical trauma (i e. wound and anastomosis).

Statistical analysis

Statistical analysis was performed using the STATGRAPHICS™ Program (Statistical Graphics Corporation, version 3 0, 1988) Non-parametric tests were used throughout and included the Mann–Whitney *U* test for comparison of mitogenic activities of plasma samples, and χ^2 test for comparison of the numbers of animals developing tumour.

Results

Growth factors in stored blood

The changes in mitogenic activity in the plasma of blood stored at 4°C for transfusion are shown in *Figure 1*. The level of growth factor activity in the plasma of blood immediately after it was taken on day 0 was approximately five times greater than the activity of serum-free medium. There was then a progressive increase in activity with duration of storage to a maximum of 15–20 times that of serum-free medium, the most significant increase occurring between 3 and 14 days ($P<0\,001$; Mann–Whitney *U* test). The variation in activity after 14 days was not significant although the trend was still upwards. By comparison, the mitogenic activity of both whole-blood serum, which contains all the platelet growth factors released during degranulation, and of outdated units of stored blood were similar.

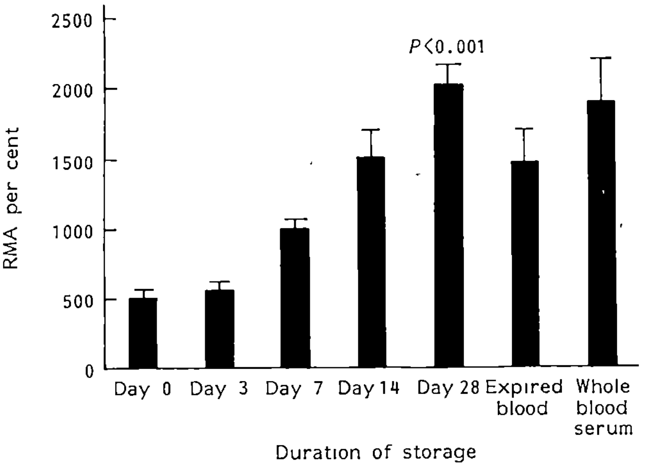

Figure 1 *Storage effect on the mitogenic activity of whole blood, mean(s e m.). RMA per cent, relative mitogenic activity*

Table 1 *Effect of serum infusion on the development of liver metastases from intraportally seeded tumour cells*

Group	No	No. with metastases	No. of metastases
Control (PBS)	25	4 (16)	2, range 2–4
Study (serum)	25	4 (16)	2, range 2–5

Values in parentheses are percentages

Growth factors and liver metastases

The effect of infusing multiple doses of serum on the outcome of intraportally seeded tumour cells is shown in *Table 1*. Of 25 animals in the control group, four developed liver metastases (16 per cent) with a median number of two metastases per liver (range 2–4). At a higher dose of tumour cells (i.e. 2–5 × 10^5 cells) the proportion of livers affected approaches 100 per cent. Therefore at this dose the threshold for tumour 'take' is attained Of the 25 animals receiving proportionately large doses of serum, the number of animals developing liver metastases was the same, with no difference in the number or size of the metastases present.

Growth factors and intraperitoneal tumour growth

The effect of multiple doses of serum infused intravenously or instilled intraperitoneally at the time of tumour seeding over a colonic anastomosis is shown in *Figure 2*. In both the control groups, receiving saline intravenously or intraperitoneally, the proportion of animals developing intraperitoneal tumour at the anastomosis or wound was not statistically different; 4/15 in the intravenous group (27 per cent) and 4/18 in the intraperitoneal group (22 per cent) These figures are similar to previous data on the effect of omentectomy on intraperitoneal tumour growth[8]. In the study group, 4/20 (20 per cent) animals receiving intravenous serum developed tumour whilst in the intraperitoneal group, 17/19 (89 per cent) developed tumour ($P<0{\cdot}01$, χ^2 test). In all groups of animals, in the absence of the omentum, the important areas for tumour 'take' were the laparotomy and anastomotic wounds.

Discussion

Controversy continues as to whether blood transfusion is an independent prognostic factor in the outcome of curative cancer surgery. Early studies, surprisingly, demonstrated an association[9,10], while others claimed that none existed and that the effect could be accounted for by other prognostic factors[11,12] A major criticism, particularly of the latter studies, was their small size, making it difficult to draw statistically significant conclusions from the available data. More recently, larger series with over 500 patients have demonstrated that the effect remains significant even after allowing for a wide range of prognostic variables

Mechanisms to explain this phenomenon have rested exclusively on an immunological basis, following the identification that renal transplants functioned longer if the patients had previously received a blood transfusion. This was supported by the demonstration that parameters of immune function, e.g. T lymphocytes and natural killer cell activity, were depressed following blood administration[13,14]. The question raised by Gantt[15] as to whether this influenced recurrence in cancer patients resulted in a number of studies into the effect of blood transfusion on experimental tumour growth. The results are highly contradictory, with some demonstrating an association[16,17], whilst others do not[5] Criticism of the positive models rests on the fact that the tumours employed were immunogenic, and that the blood transfusions were administered 1–2 weeks before tumour implantation, thus rendering the immunological environment more favourable to tumour growth[18]. Eccles *et al* demonstrated in 1980, that immunosuppression altered the behaviour of experimental tumours resulting in faster growth and greater numbers of metastases[19].

There are to date no studies which demonstrate enhanced experimental tumour growth by blood transfusion administered either at the time of implantation or in the period following. Recent clinical studies have suggested that patients who lose significant amounts of blood during surgery[1] or receive blood during or immediately after surgery[20] are at the most risk of developing recurrence. It has also been suggested that whole blood has a more deleterious effect than packed cells in terms of survival[21] In our own series of patients (unpublished data on 285 patients) we have observed that intraoperative transfusion carries the highest risk of recurrence (relative hazard 1·74; 95 per cent C.I. 1·03, 2·95) In addition, 85 per cent of those patients are transfused during this period, and 96 per cent received an average of 2 units of whole blood.

In the present study we have attempted to investigate alternative mechanisms which may account for these observations based on growth factors directly enhancing the survival of tumour cells disseminated during surgery.

Growth factors derived from degranulated platelets are the source of mitogens present in whole-blood serum and consist of epidermal growth factor, platelet-derived growth factor and β-transformed growth factor Released at sites of injury they are thought to be important in initiating the healing process and in modulating components of the immune system. Hara *et al* (1980) demonstrated that platelet growth factors could maintain the proliferation of four experimental animal tumours *in vitro* and suggested that they may be involved in the

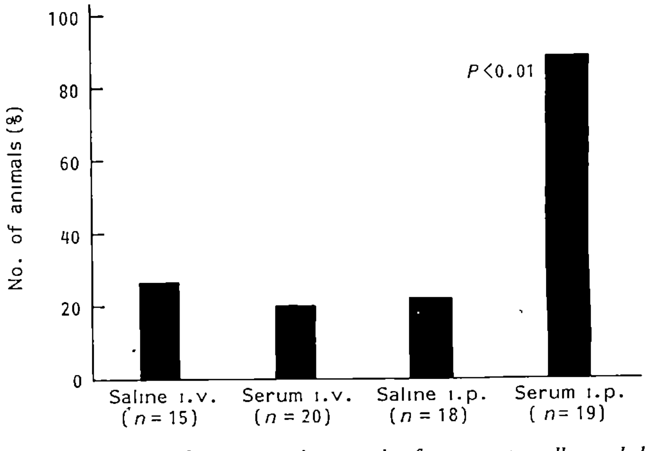

Figure 2 *Effect of serum on the growth of intraperitoneally seeded tumour cells i.v , Intravenously, i p , intraperitoneally*

metastatic process by facilitating tumour cell survival during platelet:tumour interaction[22]. Ozawa *et al* (1987) demonstrated *in vivo* that the exogenous administration of epidermal growth factor into athymic mice resulted in increased growth of subcutaneously implanted human tumours by a factor of 3–6 times[23] Although the immunosuppressive effects of platelet growth factors are being increasingly recognized[24,25], extracts from platelets have been shown to enhance experimental tumour growth *in vivo* by a direct stimulating effect rather than by immunosuppression of the host. Employing an immunologically privileged inoculation site (a hamster cheek pouch), Witkoski *et al.* demonstrated a significant increase in tumour formation in cells suspended in platelet extract compared with saline controls[26].

In our study we have demonstrated that in the plasma fraction of stored blood are growth factors which reach a maximum level after 14 days storage. This profile compares with the finding that platelets in blood, stored at 4°C, lose 75 per cent of their function by 21 days[27] It is the policy of transfusion centres to release ageing blood in preference to fresher blood, unless specifically requested. In the Wessex region the average age of a unit of blood released for colorectal cancer surgery was found to be 19 days (range 6–35 days).

The clinical significance of infusing 'mitogen-rich' plasma has yet to be determined In this study we were unable to demonstrate any alteration in the number, size or pattern of tumour occurrence in animals given large doses of whole-blood serum intravenously. This may be a reflection of the tumour employed, or that the local concentration of serum factors was not sufficiently high following dilution in the animal's whole-blood volume. However, Murphy *et al.*[28] demonstrated, with the same tumour, that very low tumour cell inocula (below that used in this study) can be stimulated to develop into metastases if the local environment is made more favourable.

The development of the animal model allowed us to investigate factors which influence the seeding of intraperitoneal tumour. Previous workers[29,30] have tended to employ large inocula of tumour cells ($1 \times 10^6 - 5 \times 10^6$ cells) and confined observations to the specific sites of tumour development only. Removal of the omentum and use of low tumour inocula make initial tumour cell survival a critical factor in the development of a recurrence. The presence of serum in the peritoneal cavity significantly enhances the development of tumour, but the mechanism for this phenomenon and the precise role of growth factors has yet to be determined. Preliminary data (unpublished) using mitogen-depleted serum (by passing over heparin–Sepharose gel) has shown that this effect is diminished However, serum is a complex fluid and it is likely that the presence of other proteins such as α_2-macroglobulin may also be responsible.

In conclusion, mechanisms to explain the phenomenon of blood transfusion-induced recurrence of cancer remain elusive. We have attempted to provide an alternative to the current immunological hypotheses based on growth factors in the plasma fraction of stored blood. However, the significance of this has yet to be ascertained.

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Mastalgia refractory to drug treatment

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Management of the patient with mastalgia who fails to respond to first line therapy is a difficult problem and there is a group of patients who do not respond to any therapy. A group of 126 patients with mastalgia who failed to respond to first line therapy and completed further treatment options was studied. The response rate of those with cyclical mastalgia fell to 57 and 25 per cent for second and third line therapy respectively. Equivalent figures for non-cyclical mastalgia were 24 and 21 per cent. Danazol maintains a high response rate after the failure of other drugs, whereas the second line response to bromocriptine and evening primrose oil is poor. Unresponsive patients were matched to a group of patients who responded to first line therapy, and reproductive and historical factors were compared using the χ^2 *test, but failed to identify which patients would respond to therapy.*

Keywords: Mastalgia, treatment, treatment failure

Mastalgia is now recognized to be a common organic condition[1]. Its classification[2–4], natural history[5] and treatment options[6,7] have been reported. Therapies which have been shown to be effective by controlled clinical trial are bromocriptine[8–10], danazol[10,11], evening primrose oil[12] and tamoxifen[13], although tamoxifen does not hold a drug licence for use in benign breast disease. To assess the response to therapies mastalgia should be classified into homogeneous subgroups. Cyclical mastalgia is an exaggeration of the normal premenstrual breast pain and tenderness which may have a hormonal aetiology[14]. Non-cyclical mastalgia is unrelated to the menstrual cycle and is less responsive to hormonal therapy. Non-cyclical mastalgia has recently been further subdivided into true non-cyclical breast pain, in which the response to hormonal therapy approaches that of cyclical mastalgia, and musculoskeletal pain, which has a lower response rate but responds well to a local injection of steroid and local anaesthetic[4]. Clinical experience has shown that in patients with cyclical mastalgia a useful response should be expected in 70 per cent of patients treated with danazol, 47 per cent treated with bromocriptine and 44 per cent treated with evening primrose oil, compared with a placebo response of 19 per cent. The equivalent figures for non-cyclical mastalgia are 31, 20, 27 and 9 per cent respectively[6]. The failure to respond to first line therapy does not preclude a response to a second treatment option. However, a small group of patients consistently fails to respond to treatment with different drugs. This may be due to a particularly resistant form of mastalgia or to poor diagnostic classification. It is important to identify this group early so that they can be spared the not inconsiderable side-effects or expense of therapy. We therefore examined whether failure to respond to an initial therapy could predict the subsequent response of the patient to other treatments and whether this group could be identified using reproductive and historical factors.

Patients and methods

In the Cardiff Breast Clinic patients with mastalgia are initially screened by examination and mammography (where indicated) to exclude malignancy, and the patient is reassured that no serious pathology has been found In the subgroup where significant pain continues, its severity and character are documented over a 2 month period using the Cardiff Breast Pain Chart and the patient is referred to a dedicated mastalgia clinic. If the pain persists despite reassurance, treatment options are discussed with the patient and one of the recognized therapies is begun or the patient is entered into an ongoing trial. The patient is reviewed 2 months after the start of treatment, and response is assessed by a combination of subjective and objective methods. Response is graded by the Cardiff Breast Score (CBS)[15] CBS I and II are regarded as being a useful response, whereas CBS III and IV represent a poor response. If a CBS I or II response has been obtained treatment is continued for a full treatment course of 6 months If danazol or bromocriptine has produced a CBS III response, treatment is continued as long as there have been no significant side-effects. If there have been side-effects or no improvement has occurred (CBS IV) treatment options are reviewed As evening primrose oil may be slow to produce a response, it is always continued for at least 4 months before treatment failure is accepted If a useful response (CBS I–II) has not been obtained after 4 months, treatment is stopped and one of the other options is substituted if the patient continues to request treatment There is a group of patients who fail to obtain improvement on treatment but feel that they can live with their symptoms, and therefore do not request a second treatment option.

Data were collected prospectively on those patients who failed to obtain a useful response (CBS III–IV) on their first line therapy and who requested and completed a second treatment option.

Between 1976 and 1988, 126 patients were identified who fulfilled these criteria, 84 had cyclical mastalgia and 42 true non-cyclical mastalgia. Patients with Tietze's syndrome and lateral chest wall pain were excluded as the treatment of these conditions differs from that of non-cyclical mastalgia The outcomes of the initial and subsequent treatment options were recorded Results were analysed with regard to the type of mastalgia and the drug of first therapeutic option Of the 126 patients, 60 completed a questionnaire about their gynaecological and reproductive history, details of their presenting complaints, past and family history of breast disease and need for subsequent breast operation were also obtained This subgroup of 60 patients was then matched by type of mastalgia and drug of first therapeutic option to 103 women who obtained a useful response (CBS I–II) to their first therapy These two groups were compared using the χ^2 test in an attempt to identify any factor which could be used to predict patients who would not respond to treatment

Results

Cyclical mastalgia

Eighty-four patients with cyclical mastalgia failed to achieve a useful response to first line therapy. Of these, 48 (57 per cent) responded to a second line therapy but 20 (24 per cent) required a third treatment option, of which only five (25 per cent) responded. The mastalgia was resistant to treatment by any of the recommended treatment options in 15 (18 per cent) of the total. Further analysis by second and third line therapies is shown in *Figures 1a–c* .

Non-cyclical mastalgia

Forty-two patients with non-cyclical mastalgia failed to achieve a response to first line therapy. Of these, 10 (24 per cent)

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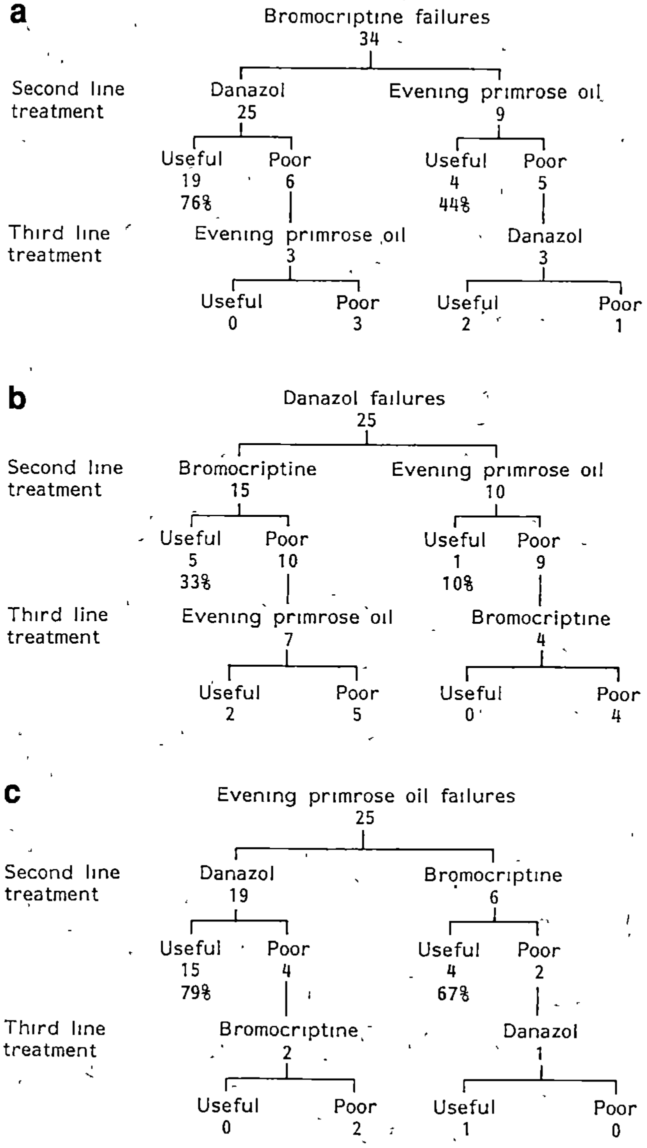

Figure 1 *Response to subsequent treatment options in patients with cyclical mastalgia:* **a** *after the failure of bromocriptine;* **b** *after the failure of danazol, and* **c** *after the failure of evening primrose oil*

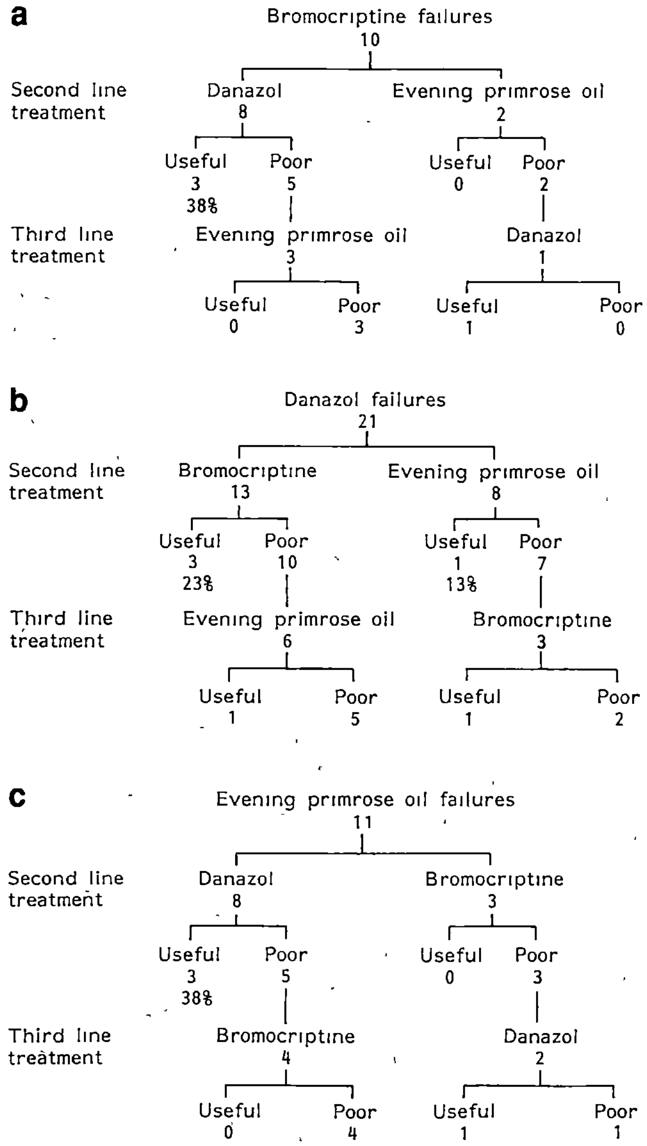

Figure 2 *Response to subsequent treatment options in patients with non-cyclical mastalgia:* **a** *after the failure of bromocriptine;* **b** *after the failure of danazol; and* **c** *after the failure of evening primrose oil*

responded to a second line therapy but 19 (45 per cent) required a third treatment option, of which only four (21 per cent) responded. The mastalgia was resistant to treatment by any of the recommended treatment options in 15 (36 per cent). Further analysis by second and third line therapies is shown in *Figures 2a–c.*

Of the 60 patients in whom reproductive and historical details were available 41 had cyclical mastalgia and 19 had non-cyclical mastalgia. These were matched to 103 patients, 80 with cyclical and 23 with non-cyclical mastalgia, who obtained a useful response to their first therapy. The two groups were matched for classification of mastalgia and the drug of first treatment option. The patients with cyclical mastalgia were analysed separately from those with non-cyclical mastalgia. No statistical difference was found between the groups for age or reproductive or historical factors.

Discussion

Hormonal manipulation, principally danazol, is confirmed as being the most effective therapy for cyclical mastalgia irrespective of treatment order. After failure on bromocriptine or evening primrose oil, danazol used as second line therapy gives approximately the same response rate as would be expected in first line treatment. For both bromocriptine and evening primrose oil the second line response rate is poor when they are used after the failure of danazol. They produce response rates similar to those which would be expected in first line treatment when used after the failure of each other. Except for danazol, the response rate to third line therapy is poor. The refractory nature of non-cyclical mastalgia to treatment is confirmed. As with cyclical mastalgia the second and third line response rates to danazol are much better than the response to either bromocriptine or evening primrose oil. It may well be that these results simply indicate poor differentiation of true non-cyclical mastalgia from apparent breast pain of other aetiologies.

The side-effects and cost of treatment can be considerable[6]. Although evening primrose oil has no significant side-effects[16], until recently it has not been available on prescription for breast disease, and cost the patient approximately £20 per month for the therapeutic dose of 3 g/day Drug side-effects are generally well tolerated where a useful response is obtained, but less well accepted when there is no improvement in symptoms. It is therefore important to predict the patients who will not respond to treatment, and two reports have indicated possible means by which this may be done. Preece *et al* showed that patients with mastalgia were no more neurotic than those with varicose veins and differed greatly from patients with recognized psychoneurosis[1] They did identify a subgroup (4 per cent of the total) who failed to respond to reassurance and at least three treatment options. These patients had scores on the Middlesex Hospital Questionnaire much closer to those of psychiatric patients. They suggested that the Middlesex Hospital Questionnaire could be used to identify patients who are likely to respond poorly to therapy. This approach has not been tested in a prospective study. Kumar *et al.* were able to show that peak, but not basal, serum prolactin levels after dynamic pituitary hormone testing correlated well with response to hormonal therapy in patients with cyclical mastalgia. A high peak prolactin corresponded to a greater response rate[17]. This relatively invasive test would be difficult to use in the routine screening of patients with mastalgia.

Comparison of patients with refractory mastalgia with those who achieved a useful response to first line therapy failed to identify any factor in their reproductive history, presenting complaints, past and family history of breast disease or need for subsequent breast operation which could reliably identify those who would achieve a useful response to drug treatment. The most useful factor in differentiating these groups is their response to danazol, a poor response indicating that the patient is unlikely to respond to bromocriptine or evening primrose oil.

Frank discussion with the patients about the likelihood of success of treatment is generally appreciated. The first treatment option is decided in conjunction with the patient. Those with severe symptoms will often request a hormonal treatment, despite the associated side-effects. These patients should be advised to try danazol as long as there are no contraindications. Where danazol is contraindicated, or the patient is not willing to risk its side-effects, particularly weight gain and menstrual irregularity, bromocriptine should be used. If danazol fails to produce a useful response bromocriptine may be tried, but is unlikely to give relief of symptoms. After failure of bromocriptine used as first line therapy, danazol should be recommended if further treatment is required. Evening primrose oil cannot be recommended as a second line treatment as its response rate is no better than would be expected from placebo or spontaneous resolution, which occurs in 22 per cent of patients with cyclical mastalgia[5]. In patients with non-cyclical mastalgia it should be remembered that careful diagnosis is of great importance as only those with true non-cyclical breast pain are likely to gain any benefit from hormonal treatment[4], and that if a treatment failure occurs careful reappraisal is required before a second treatment option is begun.

In conclusion, danazol is the most effective recommended treatment for cyclical and non-cyclical mastalgia. There are, however, a small proportion of patients who will not respond to any of the recommended therapies. These patients cannot be identified by reproductive or historical factors. Failure to respond to danazol as a first line therapy indicates that the patient is unlikely to achieve a useful response to either bromocriptine or evening primrose oil as a second line treatment Danazol may be used after the failure of bromocriptine or evening primrose oil, anticipating the same success rate as would be expected if it had been used as a first line therapy.

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Experimental study of starch-induced intraperitoneal adhesions

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The effects of starch on the development of postoperative adhesions were examined in 144 Sprague Dawley rats. Groups of rats were injected intraperitoneally with suspensions of washings from starched gloves, starch-free gloves and starch-poor washed gloves, and after operative manipulation of the bowel. The incidence of adhesions was greatest (78 per cent) after laparotomy and injections of starch-rich washings and least when starch-poor (33 per cent) or starch-free glove suspensions (37 per cent) were used, confirming an advantage for washing gloves or switching to starch-free products.

Keywords: Starch, adhesions

The incidence of intestinal obstruction due to postoperative adhesions has progressively increased over the past 50 years and it is now the commonest single cause of obstruction in the Western world[1–3]. Several factors have been implicated in the pathogenesis of adhesion formation including a peritoneal foreign body reaction to starch obtained from the surface of surgical gloves[4,5]. Starch is used to facilitate glove release from the manufacturing mould and to facilitate donning of the gloves. It was first introduced as a mould-releasing agent in 1947 by Lee and Lehman[6] to replace talc which had been demonstrated by several workers to produce a severe granulomatous reaction and adhesion formation in the peritoneal cavity[7,8]. It became evident from clinical and laboratory studies that starch was capable of producing a similar reaction, albeit less severe and less frequent[8,9].

Concern over the possible detrimental effect of starch in the abdominal cavity has led to the suggestion that surgeons should wash their gloves before surgery[10] but this recommendation conflicts with experimental evidence which suggests that washing starched gloves promotes clumping of the starch granules which, because of the consequent increase in size, are less rapidly absorbed and more likely to result in a significant foreign body reaction[11] Another option is to use starch-free gloves which have been available since 1984 The aim of this animal study was to investigate the effect of starch alone and of starch in combination with surgery on postoperative intraperitoneal adhesions and to determine the benefits of using starch-free gloves or washed starch gloves during surgery.

Materials and methods

Solutions were prepared by five washings of five pairs of sterile surgical gloves in 250 ml sterile normal saline Solution A contained the washings from five pairs of 'starch' gloves, solution B the washings from 'starch-free' gloves and solution C the suspension from five repeat washes of previously 'washed starch' gloves

One hundred and forty-four Sprague Drawley rats weighing approximately 200 g were randomly allocated to one of six experimental groups (*Table 1*) Groups 1, 2 and 3 received an intraperitoneal injection only (3 ml) of solutions A, B and C, respectively Groups 4, 5 and 6 were subjected to laparotomy. Using starch gloves, starch-free gloves and washed starch gloves, respectively, the abdomen was opened and the bowel was handled from the duodenal jejunal flexure to the rectum. The bowel was then replaced in the abdomen and the abdominal wall was closed in two layers using a continuous polyglycolic acid (Dexon®, Davis and Geck, Gosport, UK) suture Following closure of the wound, groups 4, 5 and 6 received an intraperitoneal injection (3 ml) of solutions A, B and C, respectively Although the starch in the starch-containing solutions A and C tended to settle to the bottom of the sterile container, each solution was thoroughly mixed before injection in an effort to obtain uniformity of concentrations of the starch solutions

The animals were killed after 8–10 weeks and laparotomy was performed Adhesions, if present, were assessed with regard to number and site and were biopsied Biopsies were also obtained routinely from the serosal surfaces and the inner aspect of the abdominal wall Formalin-fixed paraffin sections were prepared by standard methods and stained with haematoxylin and eosin. Sections were then examined by light microscopy including polarization The incidence of adhesions and of granuloma formation in the six groups was compared statistically using the χ^2 test with the Yates' correction factor or Fisher's exact test.

Results

There were no gross adhesions in any of the three groups which received an intraperitoneal injection only (groups 1–3) On microscopic examination of the routine biopsies, an inflammatory reaction with granuloma formation was noted in six animals in group 1, one animal in group 2, and two animals in group 3.

Gross adhesions were present in 28 of 36 (78 per cent) animals subjected to laparotomy and intraperitoneal injection of starch-rich saline (group 4). Adhesions were single in 16 animals and multiple (more than one) in 12, and the sites of adhesions included bowel to liver (18), to omentum (11), to abdominal wall (8), to bowel (2), and omentum to abdominal wall (3). Inflammatory tissue with granuloma formation was demonstrated histologically within the adhesions of all 28 animals and also on routine biopsy in one additional animal who had no gross adhesion formation. The Maltese cross appearance demonstrable on examination under polarized light and typical for starch granules was seen in the adhesions of only two of the 28 animals.

The use of starch-free gloves (group 5) or washed starch gloves (group 6) was associated with significantly fewer adhesions ($P < 0{\cdot}01$). Adhesions were single in nine of group 5 and five of group 6 animals and multiple in two of group 5 and one of group 6 animals. The sites of adhesions in group 5 animals included bowel to liver (4), to wound (4), to bowel (2), to reproductive organs (3), and omentum to bowel (2), and in

Table 1 *Outline of study groups and results*

Group	No	Solution	Laparotomy	Adhesions	Granulomata
1	20	A	–	0 (0)	6 (30)
2	20	B	–	0 (0)	1 (5)
3	20	C	–	0 (0)	2 (10)
4	36	A	+	28 (78)	29 (81)
5	30	B	+	11 (37)	13 (43)
6	18	C	+	6 (33)	6 (33)

Solution A, starch-rich; solution B, starch-free, solution C, starch-poor. Values in parentheses are percentages

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group 6 included bowel to liver (4) and bowel to wound (3). Inflammatory tissue with granuloma formation was demonstrated histologically in all adhesions in groups 5 and 6 animals and was also demonstrated on routine biopsy in two additional group 5 animals which had no gross adhesions. Starch granules were not demonstrated in any of the adhesions in groups 5 and 6.

Discussion

Concern about the presence of intraperitoneal starch relates to its clearly established role in the pathogenesis of starch peritonitis which, although exceedingly rare, is associated with a high morbidity and mortality[12–14] and to its less well defined role in the pathogenesis of postoperative adhesions[5,6]. Adhesions, although frequently seen following previous intra-abdominal surgery, are associated with intestinal obstruction in only a small proportion of cases[15]. Nevertheless, the morbidity associated with adhesive obstruction is significant and mortalities have been recorded[1–3]

The aim of the first part of the study, in which starch was injected intraperitoneally, was to determine the effect of starch alone in the peritoneal cavity uninfluenced by other factors known to promote significant tissue reaction, particularly the presence of ischaemic tissue and foreign materials such as surgical sutures[16,17]. It has been estimated that one pair of starched surgical gloves may contain up to 700 mg of starch powder[18]. By injecting the rats with 3 ml of a 250 ml solution from the washing of five pairs of gloves the maximum amount of powder administered was 42 mg per 200 g animal which is equivalent to 14·7 g per 70 kg. On the assumption that three surgeons participating in an abdominal operation do not wash their gloves beforehand and do not change gloves during the procedure, the maximum amount of starch powder deposited intraperitoneally during a standard operation is 2·1 g.

Despite the fact that the relative amount of starch deposited intraperitoneally in these animals was approximately seven times greater than in the clinical situation, no gross adhesions were seen although a histologically detectable but clinically insignificant peritoneal reaction did occur in a significant number of animals. The virginal appearance of the peritoneum in all animals in groups 1, 2 and 3 at 8–10 weeks after injection of solutions A, B and C suggests that the starch injected was completely absorbed, and this is supported by a number of previous experimental animal studies which demonstrated that starch may be absorbed as early as 48 h after surgery and that foreign body granulomata and adhesions may persist long afterwards[11,19].

The addition of laparotomy was sufficient to produce a significant number of adhesions in all three groups The surgery itself was minimally traumatic and was performed solely to expose the visceral and parietal peritoneum to the three types of glove surface. The only site that received significant trauma was the wound yet the majority of adhesions did not involve the wound. It is conceivable that the wound trauma was sufficient to reduce the level of peritoneal plasminogen activating activity (PAA). Normal peritoneum contains PAA which releases plasmin necessary for the lysis of fibrin which is deposited in the peritoneal cavity after peritoneal injury Deficiency of PAA has been implicated in the pathogenesis of adhesions[20–22] and when administered topically has been demonstrated experimentally to reduce the incidence of adhesion formation[23]. It could be argued that the high incidence of adhesion to the liver could be due to localized deposition of starch after injection in the laparotomy groups, but routine biopsies of the inner surface of the lower abdominal wall demonstrated granuloma formation consistent with foreign body reactions in all cases of adhesions. We saw no evidence of loculated fluid collections at relaparotomy suggesting that starch was distributed throughout the peritoneal cavity. The contribution of laparotomy alone was not assessed separately but the significant difference in adhesion formation between groups 5 and 6 and group 4 clearly indicated the relevance of starch in the production of adhesions.

The lower incidence of histologically detectable granulomatous foreign body reactions in group 3 animals does not support previous experimental work which suggested that washing surgical gloves before surgery, because it promotes clumping of starch granules with subsequently delayed starch absorption[11], should be avoided. Furthermore, the findings in group 3 were supported by the significantly lower incidence of adhesions in group 6 animals (washed starch gloves+laparotomy) and suggest that thorough washing of surgical gloves before surgery is beneficial. The easiest and possibly the safest option, however, is to avoid completely the use of starch gloves

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Pulse oximetry: a new non-invasive assessment of peripheral arterial occlusive disease

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Peripheral skin perfusion reflects the level of vascularity and viability of a limb and may help in planning the site of amputation or bypass surgery in patients with vascular disease. This study used peripheral pulse oximetry in 20 healthy volunteers and in 20 patients with limb ischaemia. Pulse oximetry saturation levels (P_{sa,O_2}) *were compared with ankle artery Doppler pressures and transcutaneous oxygen measurements* (P_{tc,O_2}). *Recordings were taken at two standard sites distally and referenced to finger and forearm to calculate an index. A significant correlation was found between* P_{tc,O_2} *and* P_{sa,O_2} *in patients with ischaemia* ($r = 0{\cdot}68$, $P < 0{\cdot}01$). *A further group of 12 patients with acute limb ischaemia was similarly assessed before and after revascularization. After revascularization mean(s.d.)* P_{tc,O_2} *increased from 38(13) to 44(1) mmHg* ($P > 0{\cdot}05$) *and mean(s.d.)* P_{sa,O_2} *increased from 86(3) to 90(4) per cent* ($P < 0{\cdot}01$). *These data suggest that pulse oximetry is a more sensitive index of peripheral perfusion than* P_{tc,O_2} *or ankle artery Doppler pressure and that, because of its accuracy and simplicity, it merits further use.*

Keywords: Pulse oximetry, non-invasive assessment, peripheral arterial occlusive disease

An accurate non-invasive assessment of peripheral limb perfusion is an important part of decision making in vascular surgery. Non-invasive assessment of peripheral perfusion has previously relied on clinical assessment and ankle artery Doppler pressures. Recent use of transcutaneous oxygen measurements in the limb has added a more precise estimation of tissue perfusion. It has been shown to be effective in determining a safe amputation level[1,2], in detecting peripheral arterial occlusive disease[3,4] and in predicting outcome following arterial reconstruction[5]. Despite its advantages it is not without inaccuracies. Calibration problems are frequent, as are difficulties with electrode placement and skin thickness, which may impair its reproducibility[6].

The light absorbance of oxygenated haemoglobin is different from that of reduced haemoglobin. The pulse oximeter transmits two separate light wavelengths from the emitter probe via the extremity to the sensor probe for analysis. The absorbance characteristics of oxygenated and reduced haemoglobin have a pulsatile component, which is the result of the fluctuating volume of arterial blood between the emitter and sensor probe. Tissue pulse oximetry determines arterial oxygen saturation by comparing these pulsatile changes in light transmission through an extremity at these two light wavelengths[7].

To date pulse oximetry has been found to be reproducible and effective in monitoring patients during anaesthesia and in the intensive care unit[8,9] Unlike the equipment used to measure P_{tc,O_2}, the pulse oximeter has a built-in automated calibration system and there are no problems with skin electrode placement. The electrodes can be easily clipped over the extremity or separately taped, if desired. The pulse oximeter is small in size, easy to use, and has not been used previously in the evaluation of peripheral artery occlusive disease. It was therefore the purpose of this study to compare pulse oximetry with P_{tc,O_2} and ankle artery Dopper pressure measurement in a group of healthy controls and in a group of patients with lower limb ischaemia. Changes in oxygen saturation were also assessed in patients with acute ischaemia who subsequently had revascularization procedures performed.

Patients and methods

Three groups of patients were studied. A control group of 20 healthy subjects had peripheral perfusion assessed by ankle artery Doppler pressure, P_{tc,O_2} and P_{sa,O_2} All recordings were made at room temperature in the vascular laboratory. Ankle arteries from which Doppler pressures were measured were the dorsalis pedis and posterior tibial and these were referenced to the brachial artery to calculate an ankle/brachial index Transcutaneous oxygen pressure was measured using a two-channel Kontron-632 P_{tc,O_2} recorder (Kontron Instruments Ltd, Watford, UK) and P_{sa,O_2} was measured using a Minolta Pulse/Ox-7 (AVL Medical Instruments, Schaffhausen, Switzerland) Recordings were made at two standard sites distally, (the interdigital cleft (P_{tc,O_2}) and great toe (P_{sa,O_2})) and at two proximal talar sites (the dorsum of the foot (P_{tc,O_2}) and posterior tibial area (P_{sa,O_2}). These recordings were referenced to the finger (P_{sa,O_2}) and forearm (P_{tc,O_2}) to calculate an index

A group of 20 patients with varying degrees of lower limb ischaemia was also studied Symptoms varied from a mild degree of claudication (500 yards) to acute ischaemia (rest pain). This accounts for the near normal ankle/brachial index (0·9, range 0 5–1·4) seen in this group In addition to recordings as for the control group, angiographic data were available on each patient. A further 12 patients were also studied before and after revascularization. Procedures performed were. transluminal angioplasty ($n = 3$), femorofemoral bypass ($n = 1$), femoropopliteal bypass ($n = 5$) and femorodistal bypass ($n = 3$). Angiographic data were also available on these 12 patients Angiograms were assessed using a standard grading system of distal run-off[10,11]; 2 points were given to a widely patent vessel to the ankle, 1 point for a diseased but patent vessel to the ankle, and no points for an occluded vessel, thus giving a range of 0–6. All data were analysed by univariate analysis and groups were compared using the Mann–Whitney *U* test.

Results

Ankle artery Doppler pressures, P_{tc,O_2} and P_{sa,O_2} in the control group and in the ischaemic group are shown in *Table 1* No significant correlation between these parameters was found in the control group. A significant correlation was found between P_{sa,O_2} and P_{tc,O_2} (*Figure 1*) in the ischaemic group ($r = 0{\cdot}68$, $P < 0{\cdot}01$) but not between Doppler pressures and either P_{sa,O_2} or P_{tc,O_2}. There was no significant correlation found between

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Table 1 *Oximetry, transcutaneous oxygen and ankle/brachial Doppler index results in controls and ischaemic patients*

	P_{sa,O_2} (Percentage saturation)	P_{sa,O_2} index	P_{tc,O_2} (mmHg)	P_{tc,O_2} index	Doppler index
Control (n=20)	94·8(2·5)	1·02(0·04)	61·6(6·9)	0·93(0·12)	1·03(0·04)
Ischaemic (n=20)	88·6(5·1)	0·92(0·06)	34·8(14·6)	0·60(0·24)	0·9(0·4)

All values expressed as mean(s.d.)

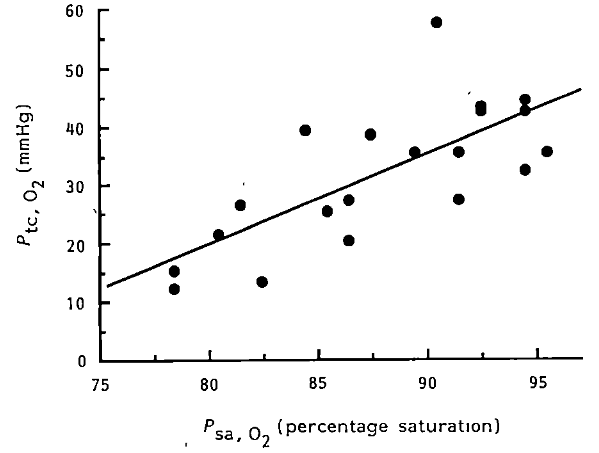

Figure 1 *Correlation of* P_{tc,O_2} *and* P_{sa,O_2} *in 20 ischaemic patients* (r=*0·68*, P<*0·01*)

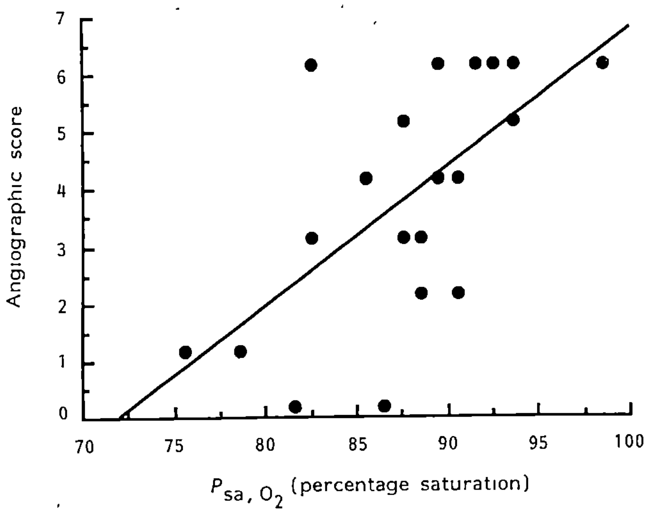

Figure 2 *Correlation of the angiographic score and* P_{sa,O_2} *in 20 ischaemic patients* (r=*0·75*, P<*0·001*)

Table 2 *Oximetry, transcutaneous oxygen, and ankle/brachial Doppler index results before and after revascularization*

	Before		After	
	P_{sa,O_2} (percentage saturation)	P_{tc,O_2} (mmHg)	P_{sa,O_2} (percentage saturation)	P_{tc,O_2} (mmHg)
Finger/forearm (control)	95(1)	60(4)	96(2)	64(3)
Posterior tibial/dorsum of foot	73(4)	48(11)	92(1)*	50(8)
Toe/interdigital cleft	86(3)	38(13)	90(4)*	44(1)
Doppler index	0·73(0·02)		0·81(0·03)	

All values expressed as mean(s.d.), $^*P<0·01$ (Mann–Whitney U test)

P_{tc,O_2} and the angiographic score in either group, but a significant correlation was found between P_{sa,O_2} (*Figure 2*) and the angiographic score in the ischaemic group of patients (r=0·75, $P<0·001$).

Recordings before revascularization and on the morning of the third postoperative day are summarized in *Table 2*. A significant correlation was again seen between P_{sa,O_2} and P_{tc,O_2} (r=0·71, $P<0·001$) but there was no significant change in the ankle/brachial index. After revascularization the increase seen in P_{tc,O_2} did not attain significance, but P_{sa,O_2} was significantly increased ($P<0·01$) A clinical and symptomatic improvement was seen in the immediate postoperative period in all patients after revascularization.

Discussion

Angiography is still the most widely used investigation in planning reconstructive surgery in patients with peripheral artery occlusive disease. Clinical examination, the measurement of ankle artery Doppler pressures and angiography are often all that are performed in the preoperative assessment of such patients. Non-invasive tests offer the surgeon a valuable supplement to angiography and subjective clinical assessment, which can be difficult and sometimes unreliable[12–14].

The measurement of ankle artery Doppler pressures has long been used by surgeons but is notoriously unreliable in assessing occlusive disease, particularly in the presence of arterial calcification[15]. Transcutaneous oxygen measurement has offered much in the non-invasive objective assessment of the peripheral circulation. Refinements such as oxygen inhalation[16] and measurements taken before and after exercise[17] have further increased its sensitivity and specificity. However, the widespread use of P_{tc,O_2} measurements can be time consuming and cumbersome. The apparatus is bulky and the recorder must be calibrated each morning with the ambient atmospheric pressure[17]. A warm-up time is required before use and preparation of the skin electrodes for each patient is complicated[4,17]. Each skin electrode must be meticulously cleansed with alcohol and a sensitive membrane applied before use. Air bubbles can accumulate underneath this membrane, which may lead to inaccurate readings, and oedematous or ulcerated skin renders recordings useless.

The tissue pulse oximeter, on the other hand, is small, durable, easily portable and does not require calibration. Skin electrodes give an instant and continuous readout of oxygen saturation levels at the bedside. The oximeter is simple to use and requires no previous experience; in the past few years it has become commonplace in the armamentarium of the anaesthetist and intensivist[7]. It provides valuable data about blood oxygenation and has been recommended as a requirement before every general anaesthetic[18]. Despite its acceptance as a successful monitor in the operating room and intensive care setting it has not been used as a non-invasive tool in the assessment of the peripheral circulation in patients with peripheral vascular occlusive disease.

This study has shown that P_{sa,O_2} can be used like P_{tc,O_2} in patients with varying degrees of disease. Its use compares favourably with that of P_{tc,O_2} but it appears to be a more sensitive index of successful reperfusion following revascularization. It correlates better than P_{tc,O_2} or ankle/brachial Doppler index with a standard angiographic scoring system and the present results suggest that P_{sa,O_2} may be a better non-invasive method of assessing the peripheral circulation than $P_{\mathrm{tc,O_2}}$ or ankle artery Doppler pressures.

Pulse oximetry has undoubted future clinical applicability in this setting, in predicting outcome following arterial reconstruction and in determining safe amputation level. Further technical developments in the skin probes will allow greater versatility and potential for its use. Because of its accuracy, reproducibility and ease of use, pulse oximetry merits further evaluation in patients with peripheral arterial occlusive disease

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Through-knee amputation in high-risk patients with vascular disease: indications, complications and rehabilitation

During a 10-year period 104 patients (mean age 72 years) had 106 through-knee amputations. Indications for surgery were: limb gangrene, 67 (64 per cent); ischaemic ulceration, 22 (21 per cent); rest pain, 9; knee contractures, 6. Thirty patients had had previous unsuccessful vascular reconstructive surgery and five had had a failed femoral embolectomy. The through-knee disarticulation used lateral skin flaps. The mortality was 21 (20 per cent). Of the 83 survivors, 59 (71 per cent) underwent uncomplicated primary wound healing; 36 (43 per cent) of the survivors were unsuitable for rehabilitation on a prosthesis. The remaining 47 (57 per cent) were walking before discharge 30–130 days (mean 68 days) after amputation. Through-knee amputation is a rapid, relatively bloodless, amputation and is a useful debridement procedure. The many surgical and functional advantages, in conjunction with the recent reports of better rehabilitation compared with the above-knee or Gritti–Stokes amputation, suggests that the through-knee amputation deserves greater consideration.

Keywords: Amputation, through-knee, indications, complications, rehabilitation

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Despite the advances in vascular reconstructive surgery it is probable that amputation will still be necessary in patients with irreversible ischaemia. Rehabilitation with a prosthesis after an amputation requires preservation of the knee joint, if at all possible, as the below-knee amputee has excellent prospects of return to full mobility[1,2]. Using the skew-flap technique[3] it is possible to perform below-knee amputation in 50–60 per cent of patients requiring amputation of an ischaemic limb.

Nevertheless, many patients require amputation at a higher level. The above-knee amputation will undoubtedly have a much higher uncomplicated healing rate than either below-knee or amputation at the knee but the above-knee amputation may be more traumatic for the patient and result in a higher mortality[4,5]. Two recent reports[6,7] have demonstrated that patients with a through-knee amputation may have significantly better functional rehabilitation on a prosthesis compared with above-knee amputees.

There has been much controversy concerning the optimal amputation at knee joint level and advantages have been claimed for both the Gritti–Stokes[8–11] and for the through-knee disarticulation[4–7,12–14]. We have used the through-knee disarticulation in the Limb Surgery Unit at Roehampton in poor-risk patients who require an urgent amputation and in patients unsuitable for rehabilitation on a prosthesis. We report the results of 10 years of through-knee amputations.

Patients and methods

During a 10-year period from January 1978 to January 1988, 104 patients had 106 through-knee amputations for vascular disease. There were 40 women and 66 men. Two main selection criteria for through-knee amputation were considered (a) extremely high-risk patients whose only chance of survival was a debridement procedure of the gangrenous limb, and (b) patients who required amputation of a lower limb and who would be non-ambulatory.

Sixty-seven patients (64 per cent) had frank gangrene, 22 (21 per cent) had ischaemic ulceration, nine (9 per cent) had rest pain and six (6 per cent) had knee joint contractures. In addition, 12 (11·5 per cent) had diabetes mellitus. In five patients gangrene was precipitated by a cerebrovascular accident with hemiplegia and in three by an acute myocardial infarction. Thirty patients had unsuccessful vascular reconstructive surgery and five further patients had had unsuccessful embolectomy. The mean age was 72·4 years (range 51–92 years).

The operative procedure was that described by Vitali *et al.*[15] using lateral skin flaps. The equal sagittal lateral flaps extend for 7 cm below the medial and lateral joint lines starting anteriorly at the tibial tubercle and extending posteriorly to 1 cm below the posterior joint line. The deep fascia is dissected with the skin to expose the joint capsule. With the knee fully flexed the ligamentum patella is detached from its insertion into the tibial tubercle and dissected back to the knee joint level. The anterior capsule and synovial membrane are cut transversely and as far laterally as possible. The cruciate ligaments are severed from their tibial insertion, leaving them as long as possible. The knee is now extended. The gastrocnemius muscles are divided from their origin near the lower end of the femur and the hamstrings are divided just below the knee joint line. The vessels can now be dissected free, ligated and divided, and the medial and lateral popliteal nerves gently pulled down and divided. The posterior capsule is divided and the amputation is complete (*Figure 1*). The patellar and hamstring tendons are sutured to the cruciate ligaments and the skin flaps closed over a drain.

All patients had peroperative antibiotics.

Results

The postoperative mortality and morbidity are outlined in *Table 1*. In nine patients death occurred within 1 week and 18 died within 30 days of surgery. Patients who died were older than the survivors (78 *versus* 71 years, $P<0·01$, Student's t test). Two of the deaths were in patients who required re-amputation to an above-knee amputation. The final outcome of the 83 survivors is shown in *Table 2*.

Diabetes had no significant effect on primary healing or on postoperative mortality.

Fourteen patients had a through-knee amputation as a revision of a below-knee amputation. Seven healed primarily and seven required revision to an above-knee amputation.

Thirteen of the survivors had had a previous contralateral amputation. Whilst a bilateral amputation is not an absolute contraindication to rehabilitation, in that five of the patients

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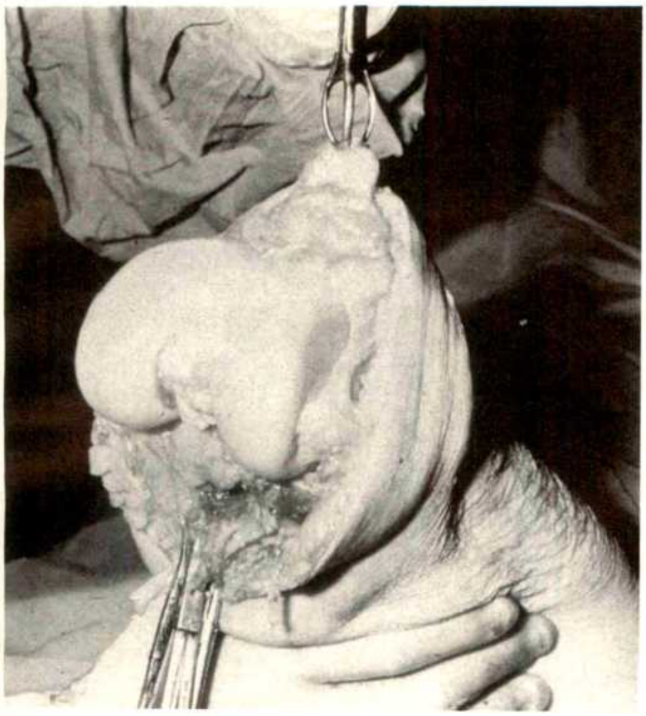

Figure 1 *Operative technique. The knee joint has been disarticulated and the lateral skin flaps have been retracted. The patellar tendon (top) and the hamstring tendons (bottom) are held before their attachment to the cruciate ligaments*

Table 1 *Postoperative mortality and morbidity*

Postoperative deaths	
Bronchopneumonia	9
Myocardial infarction	8
Cerebrovascular accident	2
Cause uncertain	2
Total	21
Re-amputation (through-knee to above-knee; 2 deaths)	14
Delayed wound healing	8
Synovial fluid collection (requiring aspiration)	4

Table 2 *Final outcome of 83 survivors*

Primary wound healing	59 (71%)
Unsuitable for a prosthesis	
Dementia/general debility	13
Hemiplegia	12
Contralateral amputation	8
Multiple sclerosis	3
Total	36 (43%)
Ambulant on a through-knee prosthesis	40
Ambulant on a above-knee prosthesis	7
Total	47 (57%)
Time to ambulation	68 days Range = 30–130 days

who walked did so on bilateral prostheses, the majority of elderly patients are unlikely to walk.

Discussion

Patients requiring urgent lower limb amputations are often both elderly and acutely ill. Commonly other vascular episodes, such as a myocardial infarction or a cerebrovascular accident, precipitate irreversible ischaemia culminating in gangrene. Though critically ill, an amputation is their only hope of survival. In this context a debridement amputation of the gangrenous area may be life-saving. However, if the patient survives, the amputation should not compromise rehabilitation either in a wheelchair or on a walking prosthesis.

A critical factor in amputation surgery is selection of the level. The factors determining early healing directly oppose the considerations of rehabilitation which are largely associated with the length of the amputation stump. There is little doubt that laboratory techniques are more accurate in predicting the likelihood of primary healing at a particular level compared with clinical assessment alone[16]. However, time may not permit their measurement and they are unavailable to many surgeons faced with an ill patient with a gangrenous lower limb. Refinements of techniques may facilitate future level selection. In this context it is notable that, of the 14 patients who had revision of a below to a through-knee amputation, only 50 per cent healed while 50 per cent required further revision to an above-knee amputation. On balance an above-knee amputation may be more appropriate.

Whilst the mortality rate of 20 per cent is high, it is a salvage rate of 80 per cent in patients who were likely to die of their diseased limb since through-knee amputations were urgent procedures to save life and accounted for less than 20 per cent of amputations in the unit, and contrasts with a mortality rate of 8·2 per cent in 256 below-knee amputations performed in the same unit[15].

The advantages of through-knee amputation in poor-risk, ill patients are that it is the least traumatic of lower limb amputations, it is relatively bloodless, it does not require bone or muscle section and can be performed under regional or local anaesthesia if necessary. The functional advantages for patients who are unsuitable for rehabilitation on a prosthesis are that stump pain is rare, and the long lever facilitates balancing and mobility when moving from the lying to the sitting position. A below-knee amputation stump may well be a hindrance in that

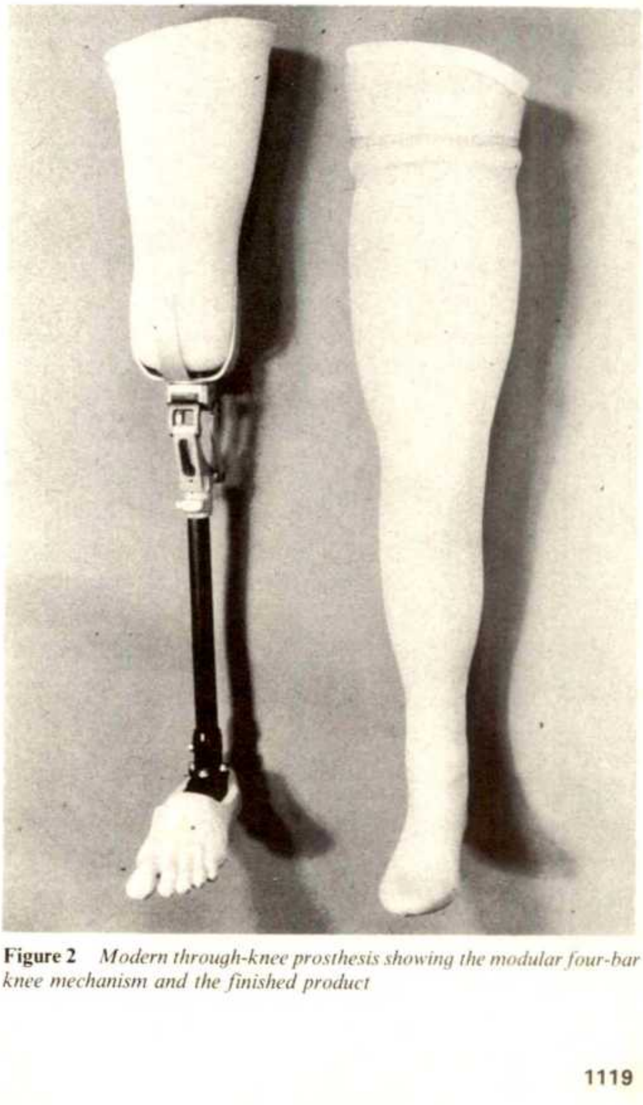

Figure 2 *Modern through-knee prosthesis showing the modular four-bar knee mechanism and the finished product*

the stump hangs down and may become ulcerated or contracted. This is especially important for bilateral amputees, as amputation through the knee joint provides a longer lever with good muscle control compared with a mid-thigh amputation.

Whilst advantages have been claimed for the Gritti–Stokes as the optimal amputation at knee joint level[8–10], many prosthetists prefer the through-knee amputation to the Gritti–Stokes amputation stump[12–15]. The functional advantages of a through-knee prosthesis are that it is a total end-bearing prosthesis avoiding ischial pressure, proprioreception is excellent, the bulbous triangular stump helps to prevent rotation and provides self-suspension for the prosthesis. Furthermore crawling is possible without a prosthesis.

One of the criticisms of the through-knee procedure is that the prosthesis is unsightly. Whilst this may be so, there have been some recent improvements in design (*Figure 2*) associated with improvement in function. Indeed, recent reports have shown that patients who had a through-knee amputiation were more likely to walk on a functional prosthesis than were patients with either an above-knee or a Gritti–Stokes amputation[6,7].

Undoubtedly, if the sole aim is primary healing of the stump, the above-knee amputation is superior to a through-knee amputation but it carries an increased mortality[4,5]. A 71 per cent primary healing rate in survivors in our series is not dissimilar to that of the reported uncomplicated healing rate of Gritti–Stokes. Our results demonstrate that through-knee amputation has a reasonable chance of primary healing and that fit survivors can be rehabilitated on a prosthesis. This amputation deserves greater consideration in poor-risk patients who require an urgent amputation for limb gangrene and in patients who are unsuitable for rehabilitation on a walking prosthesis.

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Effect of surgery on the systemic inflammatory response to intermittent claudication

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The hypothesis that intermittent claudication initiates a systemic inflammatory response was investigated by studying the effect of exercise on markers of neutrophil activation and vascular permeability in 25 claudicants and 10 controls. Urinary albumin excretion, previously demonstrated to reflect vascular permeability, increased significantly after exercise in claudicants and was associated with decreased neutrophil filterability and increased serum lysozyme activity. No similar exercise-induced changes were seen in controls or in claudicants after successful arterial bypass surgery. These results suggest that intermittent claudication is associated with potentially deleterious systemic manifestations that are surgically reversible.

Keywords: Ischaemia, albuminuria, neutrophils

It is accepted that severe tissue ischaemia can have adverse systemic effects[1,2]. There is increasing evidence suggesting that lower limb ischaemia can initiate a systemic response in which inflammatory mediators (such as thromboxane A_2) activate neutrophils[3,4], leading to endothelial cell damage and an increase in vascular permeability[5,6]. Neutrophils (polymorphonuclear leucocytes, PMN) can induce vascular damage by the release of oxygen-derived free radicals (ODFR)[7].

Stimulated leucocytes show an impaired ability to flow through small-pore filters and this reduced filterability has been used to demonstrate PMN activation after severe ischaemia[4]. An increase in the serum concentration of lysozyme (a neutrophil granular enzyme) indicates the degranulation of neutrophils after activation by an inflammatory stimulus[8].

Low-level albuminuria (microalbuminuria) is undetectable by qualitative 'stix' tests but is associated with a number of acute inflammatory conditions[9]. It is likely that an increase in glomerular permeability to albumin reflects a generalized increase in vascular permeability to macromolecules[9]. Microalbuminuria can be precipitated by exercise in patients with intermittent claudication and is asssociated with an increase in ODFR activity[10].

It is possible that transient ischaemia, associated with intermittent claudication, induces a systemic reaction involving PMN activation and an increase in vascular permeability. This study set out to investigate this hypothesis and to determine whether any systemic changes observed were reversible by bypass surgery.

Patients and methods

Local ethical committee approval was obtained for the study. Twenty-five patients (22 men and 3 women) of mean age 66 years (range 49–80 years) with intermittent claudication were investigated. Claudication had been previously diagnosed by history, a resting ankle–brachial pressure index (ABPI) of $<0{\cdot}8$ and an ankle systolic blood pressure fall of >30 mmHg after a standard 1 min exercise test[11]. The time taken for ankle pressure to return to the resting level (pressure recovery time, PRT) was also recorded. Ten healthy volunteers (9 men and 1 woman) of mean age 62 years (range 51–81 years), in whom claudication was excluded by ABPI measurement and exercise testing, acted as controls. All patients and controls were normotensive, non-diabetic and had a normal serum creatinine.

Having emptied their bladders, subjects rested for 1 h then emptied their bladders again, producing a specimen of mid-stream urine (MSU). Subjects then walked at 3 km/h on a treadmill with a 10° incline, claudicants until stopped by pain and controls for 4 min (the mean walking time of the claudicant group). After a further 1 h rest a second MSU was obtained.

In addition, claudicants being considered for bypass surgery and controls had blood taken from a forearm vein via an indwelling cannula immediately before exercise and again 15 and 60 min afterwards.

The tests were repeated 3 months after operation on 12 patients who underwent successful surgery, determined by a reduction in symptoms and restoration of ABPI to above 0·9. The patients walked the same distance as they had done before surgery.

Urinary albumin was measured by radioimmunoassay (Diagnostic Products Corporation, Wallingford, UK) and was expressed as the urinary albumin–creatinine ratio (ACR) in mg/mmol to compensate for changes in urinary flow during the investigation.

Neutrophil filterability was estimated by the ability of a granulocyte suspension to flow through a 5 μm pore filter. A pellet of granulocytes (>97 per cent neutrophils) was separated from heparinized blood by gradient density centrifugation and corrected to a constant concentration of $1{\cdot}4 \times 10^9$ cells/l. This suspension was then allowed to fall under hydrostatic pressure through a polycarbonate filter and the cumulative volume of filtrate collected was recorded at 10 s intervals for 90 s. Cumulative volume plotted against log time produced a straight line ($r > 0{\cdot}99$ on all occasions) from which the flow rate was calculated in ml/min. Neutrophil viability was greater than 98 per cent as estimated on trypan blue exclusion. The reproducibility of the technique was assessed by taking duplicate blood samples through the whole procedure; flow rates for each duplicate differed by less than 7 per cent.

Serum lysozyme activity was determined on a Mira discretionary analyser (Hoffman-La Roche and Co. Ltd., Diagnostica, Basle, Switzerland) using a suspension of *Micrococcus lysodeikticus* in pH 6·2 phosphate buffer standardized against purified egg white lysozyme (Sigma Chemical Co. Ltd., Poole, UK).

Mean (range) values for ACR, neutrophil filterability and serum lysozyme were calculated and differences between groups compared using the Wilcoxon signed rank test.

Results

The mean (range) resting ACR in claudicants of 4·1 (0·2–34·6) was significantly higher than the mean of 0·8 (0·3–2·8) for the control group ($P < 0{\cdot}001$). After exercise, mean ACR increased in claudicants by 167 per cent to 9·0 (0·2–48·1) ($P < 0{\cdot}001$) but there was no significant change with exercise in the control group, mean 0·8 (0·2–2·1). There was a positive correlation between ankle PRT and the percentage change in ACR that occurred after exercise in the 25 claudicants (*Figure 1*). The correlation between the change in ACR and the initial fall in ankle pressure was not so convincing ($r = 5{\cdot}7$, $P < 0{\cdot}05$).

Before operation, ACR in the 12 patients who underwent bypass surgery increased from 4·8 (0·2–18·5) to 13·9 (0·2–48·1) after exercise (*Figure 2*). A logarithmic scale was required to display these data graphically owing to the considerable variation in absolute ACR values. Changes in ACR, mean

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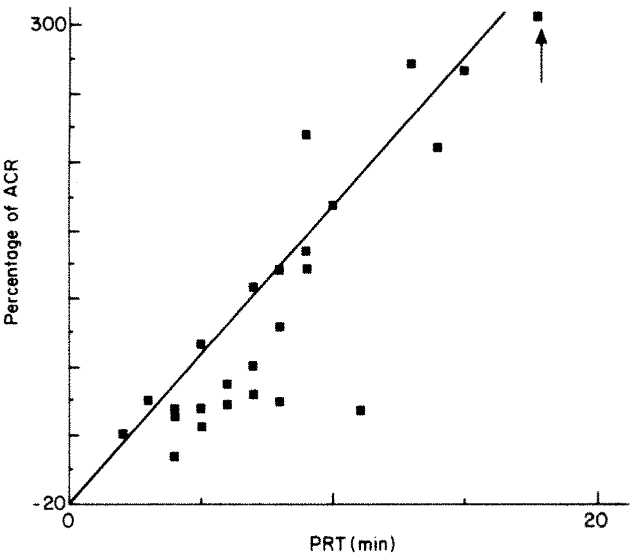

Figure 1 *Ankle pressure recovery time (PRT)* versus *percentage change in albumin–creatinine ratio (ACR) after exercise in 25 claudicants.* P *<0·01,* r *= 0·67*

186 per cent (20–2155 per cent), therefore tend to appear small. The mean resting ACR after surgery, 4·4 (0·5–24·8), was not significantly different from the preoperative value, but the increase with exercise was reduced to 6·7 (0·4–27·2) and this trend was observed in all 12 patients (*Figure 2*).

There was no significant difference in neutrophil filterability between resting claudicants and controls. Filterability was reduced, however, in all 12 claudicants 15 min after exercise, but had risen towards resting values by 60 min. There was no change in PMN filterability with exercise in controls or in the claudicants when the tests were repeated after bypass surgery (*Figure 3*).

Serum lysozyme activity increased in claudicants 15 min after exercise. No such exercise-induced increase was found after operation or in the control group (*Figure 4*).

Discussion

Following exercise, ankle PRT is related to limb blood flow[12] and in the authors' experience is a more reproducible assessment of claudication than the initial fall in ankle pressure[13]. The positive correlation between PRT and the increase in ACR after exercise suggests urinary albumin excretion is related to the severity of claudication. It also suggests that intermittent claudication is associated with an

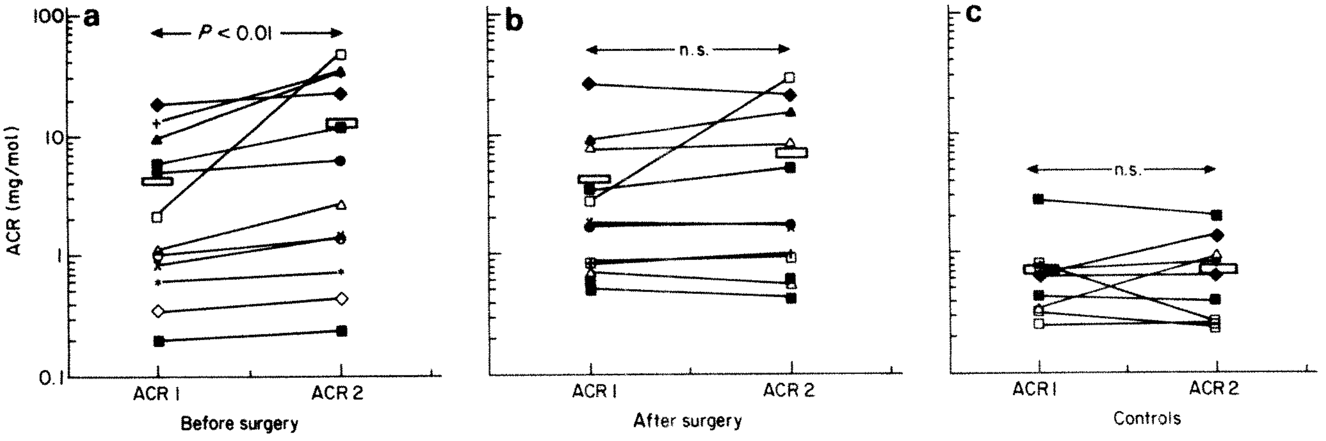

Figure 2 *Urinary albumin–creatinine ratio (ACR) before (ACR1) and after (ACR2) exercise in claudicants:* **a** *before surgery,* **b** *after surgery and* **c** *in controls, plotted on a log scale.* ▭*, mean*

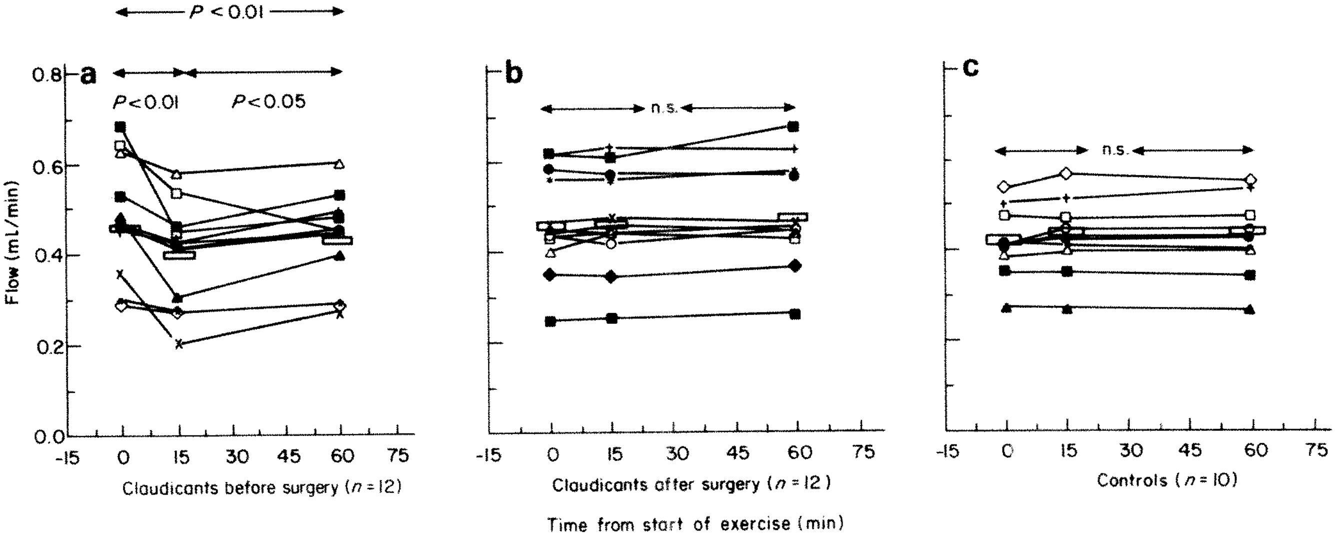

Figure 3 *Change in neutrophil filterability with exercise in claudicants:* **a** *before surgery,* **b** *after surgery and* **c** *in controls.* ▭*, mean*

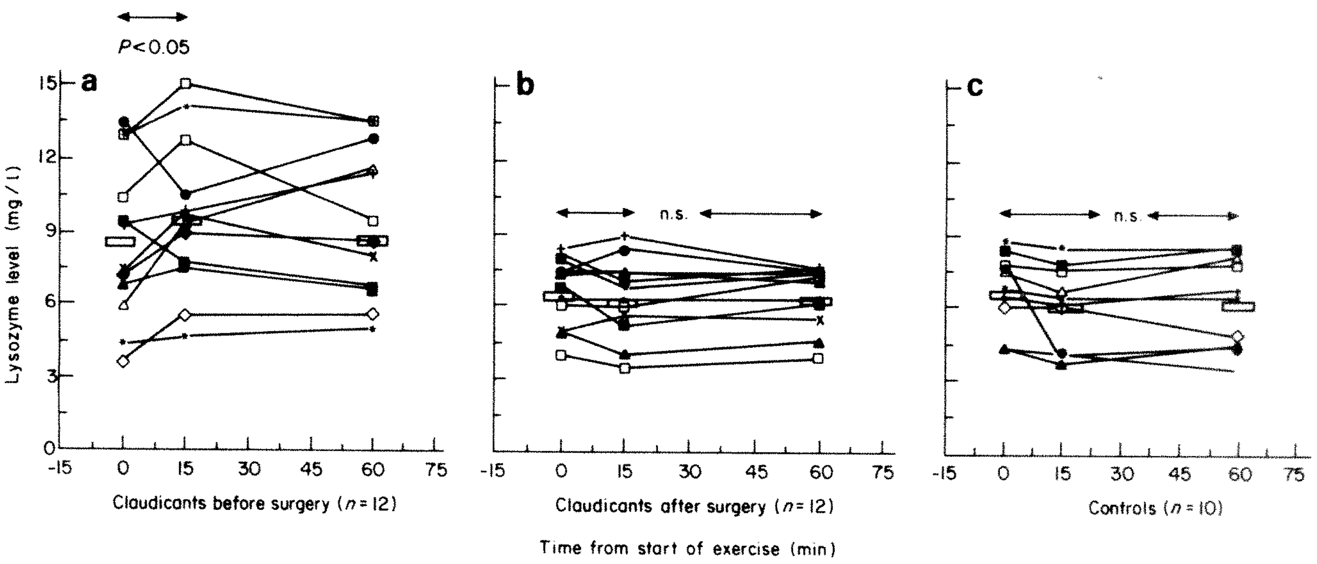

Figure 4 *Change in serum lysozyme level with exercise in claudicants:* **a** *before surgery,* **b** *after surgery and* **c** *in controls.* ▭, *mean*

increase in vascular and renal permeability to albumin that is proportional to the degree of ischaemia.

Neutrophil-mediated vascular injury occurs upon reperfusion following severe ischaemia[14] and recent studies suggest that moderate ischaemia can also incite a similar reaction. Erlansson *et al.*[15] showed that incomplete ischaemia produces a microvascular response similar to that of complete ischaemia in the hamster cheek pouch model. Furthermore, there is a rise in serum thromboxane A_2[16] and urinary thromboxane metabolites[17] after exercise in patients with intermittent claudication and an increase in serum lipid peroxide levels, suggesting ODFR activity, in claudicants following exercise has previously been reported[10]. The present study provides evidence of exercise-induced neutrophil activation. This supports the hypothesis that transient ischaemia, associated with claudication, elicits a systemic response in which inflammatory mediators activate neutrophils, leading to endothelial cell damage and an increase in vascular permeability. Work is continuing into the mechanisms and pathological significance of this phenomenon, using an animal claudicant model.

The present results may help to explain the prolonged 'acute-phase' reaction that is associated with vascular disease[18], and the association of hypoalbuminaemia[19] and proteinuria[20] with increased cardiovascular mortality. Neutrophilia is associated with an increased risk of atherosclerotic complications while neutropenia appears to offer protection[21]. Many data support a vital role for granulocyte–endothelial cell interaction, lipid peroxidation and increased vascular permeability in the pathogenesis of atherosclerosis[22–24]. Exercise-induced neutrophil activation and increased vascular permeability may, therefore, accelerate atherogenesis and thus contribute to the high mortality that is associated with intermittent claudication[25].

The finding that the systemic effects of claudication were surgically reversible could have therapeutic implications. Currently, claudicants are encouraged to exercise and intervention is usually reserved for severe, progressive symptoms, or the development of critical ischaemia. Although exercise may increase walking distance, the present results suggest that it could exacerbate systemic vascular injury. Repeated inflammatory episodes induced by claudication could result in permanent damage, which would explain the finding of an elevated ACR in resting claudicants. Should this prove to be pathologically significant, surgical intervention would be required at an earlier stage, particularly as minimally invasive techniques are becoming available. Moreover, putative treatment regimens require evaluation, as those which reverse the systemic response to claudication may be preferred to those offering merely symptomatic relief.

In conclusion, the present data demonstrate that potentially deleterious systemic manifestations of intermittent claudication are reversible by bypass surgery. The effect of early surgical intervention on subsequent cardiovascular morbidity and mortality should now be determined by a controlled trial.

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Graft stenosis: justification for 1-year surveillance

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In all, 412 femorodistal grafts (femoropopliteal and femorocrural), performed between 1984 and 1988, have been prospectively studied at 6 weeks and 3, 6, 9 and 12 months after operation and at intervals of 6 months thereafter by duplex scanning and intravenous digital subtraction angiography. The overall incidence of stenoses was 16 per cent (femorocrural 20 per cent, femoropopliteal 15 per cent). All stenoses were detected in the first year after operation and none occurred after this. Twenty-four non-haemodynamically significant stenoses were not treated but were followed at intervals of 3 months. Forty-two haemodynamically significant stenoses were detected and secondary procedures were performed in 30 grafts at a mean of 8 months after surgery. Thirteen had percutaneous balloon dilatation and six (46 per cent) remain patent at a mean follow-up of 22 months. Two grafts which occluded within 30 days and three which restenosed at a mean of 8 months had tertiary procedures. Seventeen grafts were surgically revised, nine with patch grafts and eight with bypass grafts. Eleven of these remain patent at a mean follow-up of 30 months. One occluded immediately and three occluded late. Two grafts which restenosed at a mean of 19 months had successful tertiary procedures. In total, seven grafts had tertiary procedures (two had balloon dilatation and five had surgery) and six of these remain patent at a mean follow-up of 13·5 months. In conclusion, 37 procedures have been performed on 30 grafts, of which 23 (77 per cent) remain patent at a mean follow-up of 12 months. Approximately one-quarter of femorodistal grafts will develop graft-related stenoses and graft surveillance is worthwhile, but only for the first year after operation.

Keywords: Artery, graft, stenosis

Most studies agree that stenoses occur in approximately one-quarter of femorodistal grafts[1–6] and represent an important and potentially treatable cause of graft failure. If it is accepted that graft failure during the first month is caused by errors of technique or judgement, that failure after 2 years is the result of progression of proximal or distal atherosclerosis, and that failure between 1 month and 2 years is graft related, then approximately 80 per cent of graft occlusions are the result of graft-related stenoses[7]. Many patients with graft stenoses are asymptomatic and clinical examination alone cannot reliably detect haemodynamically compromised grafts which remain patent[5]. Screening techniques are therefore necessary to diagnose and assess the severity of stenoses.

The simplest method is Doppler arterial pressure assessment at the ankle, with or without exercise testing. Unfortunately there are now many studies that reveal the inadequacy of this form of screening[8–10].

Duplex scanning and intravenous digital subtraction angiography (IVDSA) are more sensitive in detecting stenoses but are both expensive and time consuming. The screening programme therefore needs to be rationalized and justified. Screening of all vein and synthetic femorodistal grafts (both popliteal and crural) has established first the incidence of stenosis in various types of grafts, second the validity of duplex and DSA examinations in diagnosing stenoses, and finally the optimum timing of follow-up investigations. This surveillance programme has been combined with revision of haemodynamic stenoses, and the results of these procedures are presented.

Patients and methods

Screening

In all, 412 femoropopliteal and femorocrural grafts, inserted between 1984 and 1988, have been prospectively studied with duplex scanning and IVDSA at 6 weeks and 3, 6, 9 and 12 months after operation and at intervals of 6 months thereafter. The entire length of the graft was studied with a 7·5 MHz probe (Diasonics, Bedford, UK, 300DRF) and latterly with colour flow imaging (Philips Medical Systems (UK) Ltd., London, UK). Stenosis was defined as an increase in velocity of 50 per cent or more within a 2 cm length of graft[6]. Stenoses were subdivided into two groups. The first group consisted of non-haemodynamically significant stenoses which were defined as those with a peak velocity increase of between 50 per cent and 100 per cent, with a 30–50 per cent stenosis on IVDSA. The second group consisted of haemodynamically significant stenoses with greater increases in peak velocity and >50 per cent stenosis on IVDSA.

Treatment

Non-haemodynamically significant stenoses were kept under review, but no intervention was undertaken. Haemodynamically significant stenoses were repaired. Web stenoses were treated with percutaneous transluminal balloon dilatation, using a soft 2·5 cm cardiac balloon with pressures of 15 atmospheres (*Figure 1*). Short stenoses were surgically treated with a vein patch (*Figure 2*). Longer stenoses and those located adjacent to anastomoses were treated with a bypass graft using arm vein for vein grafts or polytetrafluoroethylene (PTFE) for synthetic grafts.

Statistical methods

The statistical significance of differences in results was assessed by χ^2 analysis.

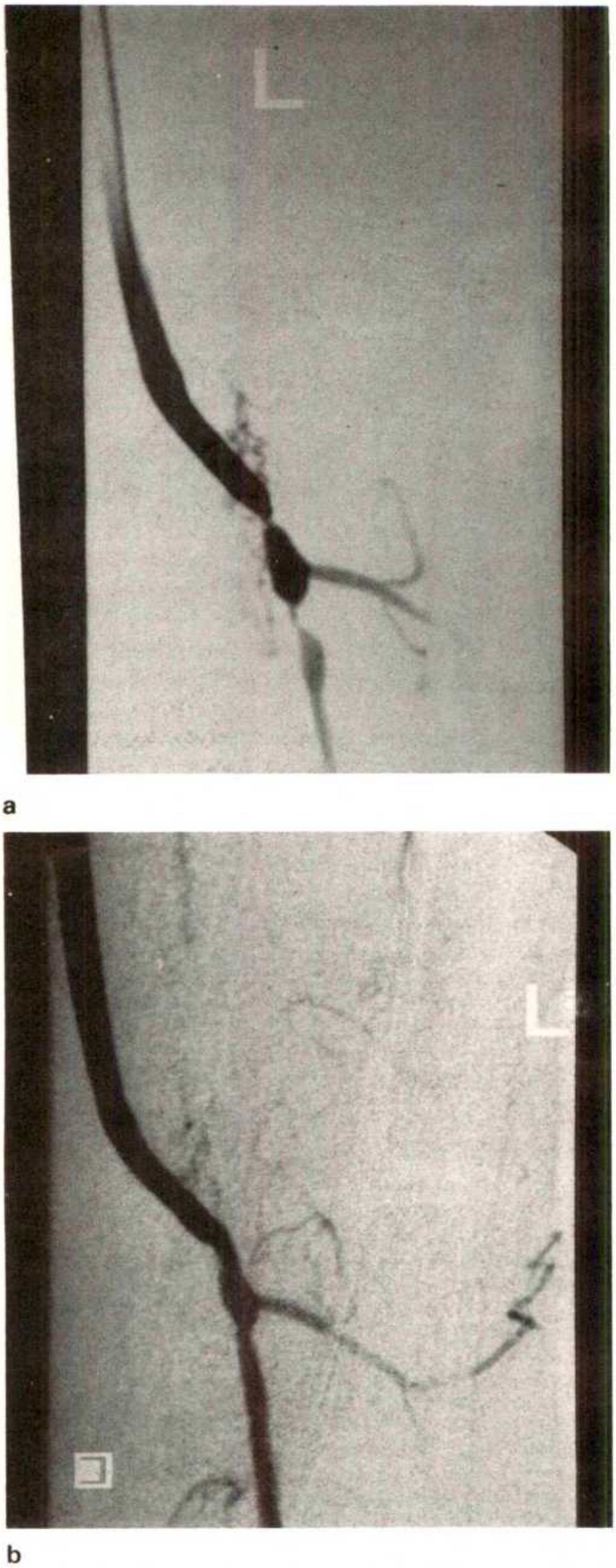


Figure 1 **a** *Stenoses at the heel and toe of the distal anastomosis of a vein femoropopliteal graft 8 months after insertion.* **b** *Both stenoses have been treated by balloon dilatation*

Results

Grafts assessed

In all, 412 grafts were assessed and comprised 290 (70 per cent) femoropopliteal grafts, and 122 (30 per cent) femorocrural grafts. Of these, 214 (74 per cent) of the femoropopliteal grafts were composed of vein conduits and 76 (26 per cent) of PTFE. Eighty-seven (71 per cent) of the femorocrural grafts were vein and 35 (29 per cent) were PTFE. PTFE was used in preference for above knee grafts to preserve the vein for future distal grafts, and PTFE crural grafts were inserted in patients in whom previous reconstruction and coronary artery bypass grafting rendered suitable lengths of autologous arm or leg vein unavailable.

Investigation

Sixty-six (16 per cent) of the 412 grafts developed a stenosis at a mean follow-up of 22 months (range 9–48 months).

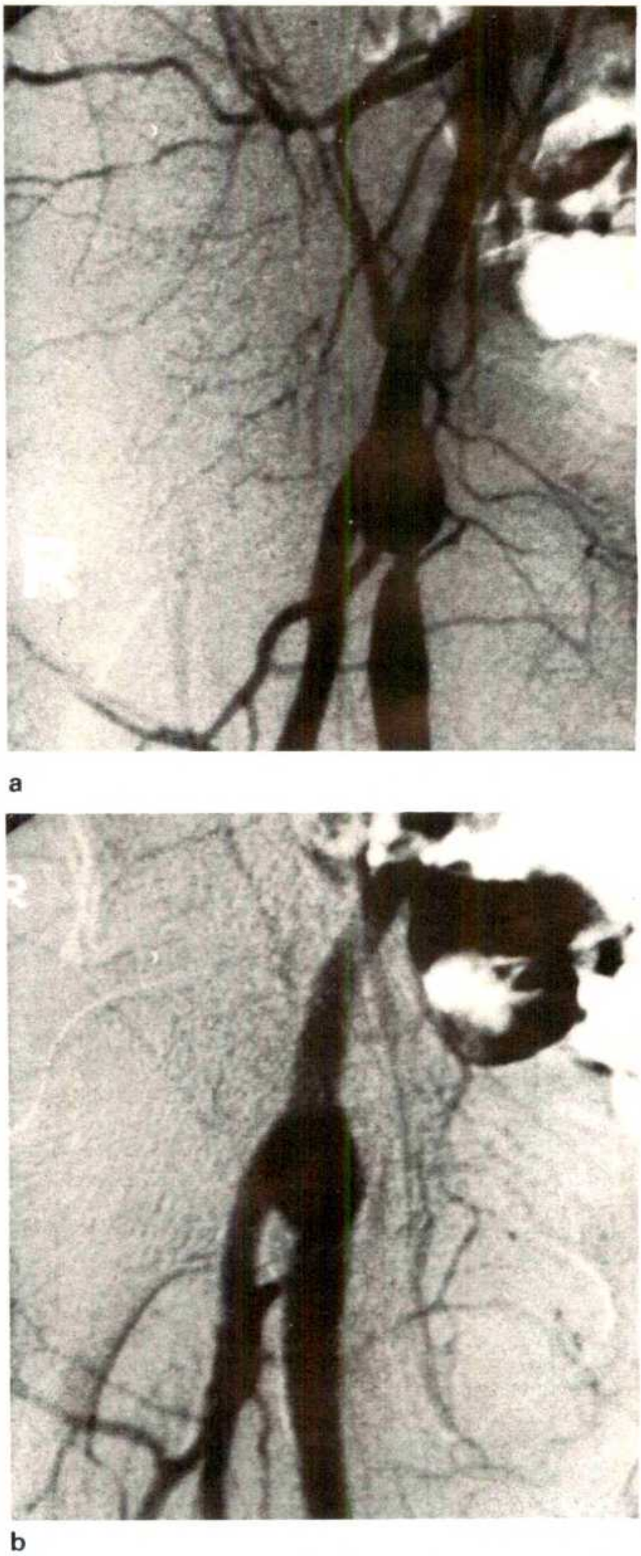


Figure 2 **a** *Stenosis just distal to the proximal anastomosis.* **b** *Result following vein patch angioplasty*

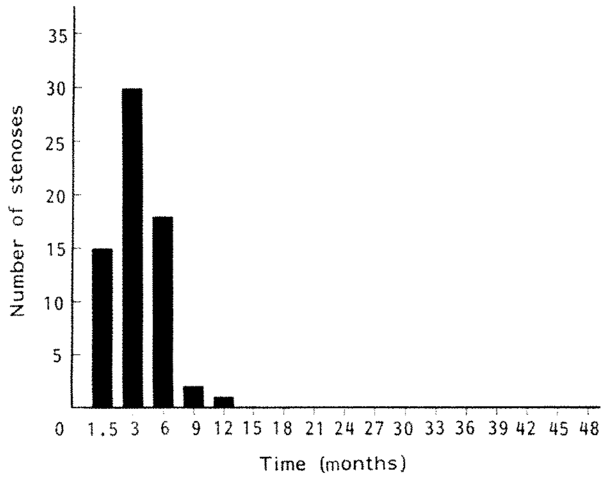
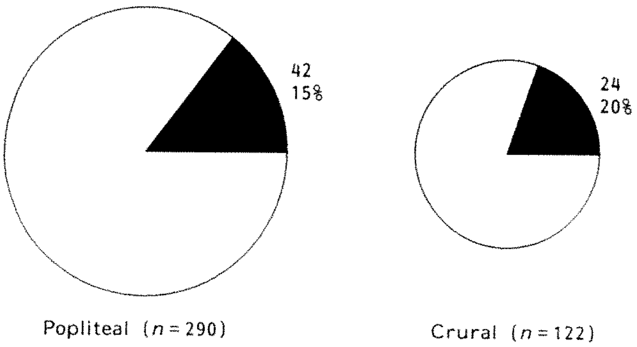


Figure 3 *Numbers of grafts developing new stenoses at various time intervals after surgery*



Popliteal ($n = 290$)   Crural ($n = 122$)

Figure 4 *Graft-related stenoses in 412 femorodistal procedures*

Twenty-four stenoses were non-haemodynamically significant and 42 were haemodynamically significant. Twenty-two stenoses occurred adjacent to the distal anastomosis, 13 adjacent to the proximal anastomosis and 31 in the body of the graft. In four other patients duplex scanning suggested a stenosis at the knee which was not confirmed by IVDSA. Duplex incorrectly indicated stenoses at the distal end of the graft in four patients; IVDSA showed these to be located in the distal native vessels away from the anastomoses. Duplex showed a stenosis in one graft which was not shown by IVDSA. This was subsequently confirmed at operation to be a web stenosis. The number of grafts first developing a stenosis at each time interval following surgery is shown in *Figure 3*. Sixty-three per cent of stenoses appeared within 6 months. No stenoses were detected after 1 year.

The number of grafts with a stenosis in each group is shown in *Figure 4*. There was a higher incidence of stenosis in femorocrural grafts (20 per cent) than in femoropopliteal grafts (15 per cent), but this difference was not statistically significant. Vein conduits were more likely to have stenoses detected (19 per cent) than synthetic grafts (7 per cent, $P < 0.003$). Thirty-five stenoses were found in 214 femoropopliteal vein grafts giving an incidence of 16 per cent; in comparison only seven stenoses were found in 76 PTFE femoropopliteal grafts (9 per cent). The highest incidence of stenosis was found in femorocrural vein grafts of which 23 of 87 (26 per cent) were affected. In contrast, the lowest incidence was found in PTFE femorocrural grafts in which only one of 35 was detected. However, the occlusion rate of PTFE grafts remains higher than for vein grafts which suggests that the diagnosis and treatment of PTFE graft stenoses may have less effect on patency rates.

Treatment

No procedure was undertaken in the 24 grafts with non-haemodynamically significant stenoses. Three of these occluded. Of the 42 grafts with haemodynamically significant stenoses, two occluded. One of these occluded before the patient's admission to hospital for planned surgical correction of the stenosis, and the second was in a patient who refused further follow-up. At the time of assessment 30 grafts had been revised (*Figure 5*) and the remaining ten grafts were to have secondary procedures. Twenty-five of the grafts repaired were vein conduits (14 femoropopliteal and 11 femorocrural). Only five synthetic grafts were repaired (four femoropopliteal and one femorocrural). Thirteen patients had percutaneous transluminal balloon dilatation. Six of these grafts remain patent at a mean follow-up of 15·5 months. Two grafts which occluded within 30 days and three which restenosed at a mean follow-up of 8 months had tertiary procedures.

Seventeen grafts were surgically revised (*Figure 5*). Nine patch grafts have been performed for stenosis in the body of grafts. Eight bypass grafts have been performed for stenoses around the proximal and distal ends of grafts. Eleven of 17 grafts remain patent at a mean follow-up of 9 months. One graft occluded immediately and three occluded late. Two grafts restenosed at a mean of 19 months and had successful tertiary procedures.

In total, seven grafts had tertiary procedures (two had balloon dilatation and five surgery). Six of these remain patent at a mean follow-up of 13·5 months.

To date, 37 procedures, 15 balloon dilatations and 22 operations have been performed on 30 grafts, of which 23 (77 per cent) remain patent at a mean follow-up of 12 months.

Discussion

The failure rate for femorodistal grafts is highest within the first 2 years after operation[7,11]. Graft-related stenoses have been recognized as a significant factor in graft failure during this time and represent a potentially treatable cause of graft thrombosis[7,12]. Salvage procedures performed on patent grafts are associated with much better results than those undertaken for occluded grafts[7]. Therefore, early detection and aggressive treatment of severe stenoses should increase graft patency rates[5]. This study was undertaken to assess both the incidence of stenoses in femorodistal grafts and the results of treatment. With this information it was hoped to rationalize this unit's surveillance programme.

The overall incidence (16 per cent) of grafts developing a stenosis is compatible with previous reports[1–3,5,6,8,9,13]. If ankle:brachial systolic pressure measurements alone are used as a screening procedure to select patients for arteriography, the reported incidence of stenosis is much lower, at 9 per cent[4]. Duplex scanning is a sensitive test for the recognition of stenoses, and the magnitude of velocity changes correlates well with the severity of narrowing found on IVDSA[14]. This unit's initial experience with duplex assessment was unsatisfactory

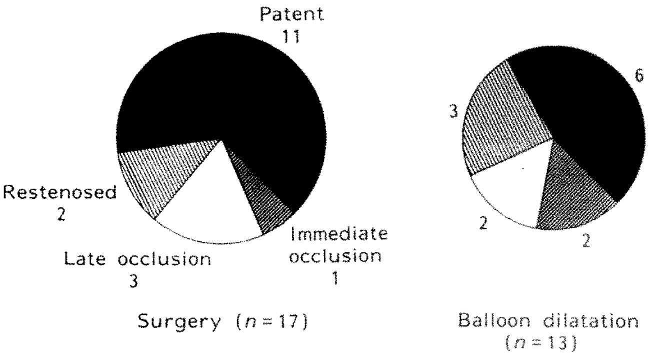


Figure 5 *Results of secondary procedures for graft-related stenoses*

because it depended on graft blood flow. This measurement was found to be unreproducible within the graft itself and from one observer to another[15]. Furthermore, the use of graft blood flow is unreproducible from one visit to the next since cardiac output and peripheral resistance affect blood flow. Measuring the change in velocity across a short segment eliminated these confounding factors and such measurements were highly reproducible.

The higher incidence of stenoses in femorocrural grafts compared with femoropopliteal grafts in this study is similar to those previously reported by Bandyk *et al.*[16] and Berkowitz *et al.*[3]. Berkowitz *et al.* reported an incidence of 29 per cent in femorocrural grafts compared with 8 per cent for femoropopliteal grafts.

Ninety-five per cent of the stenoses found in the present study were first diagnosed within 6 months of operation and all within 1 year. Berkowitz *et al.*[3], using longer time intervals between tests, diagnosed 77 per cent of 30 stenoses by 1 year. However, they also found stenoses which first appeared at 3, 4, 5 and 8 years at a rate of one to two per year. Disselhoff *et al.* also reported five stenoses first appearing between 12 and 29 months[13]. Neither of these reports makes it clear whether the grafts that developed late stenoses were carefully assessed during the first year after operation. Present data suggest that, if a policy of strict surveillance during the first year after operation is adhered to, further duplex surveillance is not justified.

Before graft stenoses were systematically studied, surgeons assumed that the majority of problems arose at the distal anastomosis. However, present findings that 33 per cent occur proximally and 47 per cent occur in the body of the graft is supported by other series[3,8,16]. Those stenoses causing less than 50 per cent diameter reduction were monitored at intervals of 3 months. Some, but not all, progressed to become haemodynamically significant[14]. Even haemodynamically significant stenoses may not produce clinical symptoms or a reduction in ankle arterial pressure[8].

The policy of operating upon only haemodynamically significant stenoses has meant that three of 24 non-haemodynamically significant stenoses have occluded while under observation. Thirty grafts of 42 with haemodynamically significant stenoses have undergone further procedures to maintain patency. The overall patency rate in these treated grafts is 77 per cent at a mean follow-up of 12 months, which is similar to the results reported by Berkowitz *et al.*[3]. The results of surgical intervention appear to be similar in the various reported series, although follow-up period is variable. The resulting patency rate of at least 75 per cent implies that this interventional policy is justified. If no procedure is undertaken, grafts with significant stenoses have a much higher rate of occlusion than those without a stenosis[17].

Others have reported more encouraging results with balloon dilatation of grafts[7,18]. The use of high pressures (15–20 atmospheres) is important but the authors believe that only web stenoses and very short segment stenoses should be treated in this way. The balloon dilatation of longer stenoses may have led to the very discouraging results in some centres[9].

This prospective study of over 400 patients has confirmed that duplex examination of femorodistal grafts is an effective screening technique for the detection of stenoses which occur in approximately 20 per cent of such grafts. While routine IVDSA is not necessary, it is mandatory before reconstruction, not only to confirm the presence of a stenosis but also to provide anatomical information for possible reconstructive procedures. Both balloon dilatation and surgery are successful methods for graft revision, and the present results support the view that short web stenoses may be treated successfully by balloon dilatation. Longer stenoses are better treated surgically using either a patch technique or, more often, by a limited bypass graft.

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Recent changes in the treatment of aortoiliac occlusive disease by the Oxford Regional Vascular Service

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Over the four years from 1 January 1985 to 31 December 1988, 192 patients were treated for aortoiliac occlusive disease by the Oxford Regional Vascular Service. The number of patients treated by percutaneous transluminal angioplasty increased from two in the first year of the study to 34 in the third year of the study. This increase was accompanied by a decrease in the proportion of patients treated by aortobifemoral bypass but the proportion of patients treated by extra-anatomic bypass remained constant at around 30 per cent. Twice as many patients were treated in the fourth year as in the first year of the study so that the number of surgical operations increased despite many patients being treated exclusively by percutaneous transluminal angioplasty. The number of patients requiring mandatory treatment for limb salvage increased by 109 per cent and optional treatment for intermittent claudication by 85 per cent. The introduction of percutaneous transluminal angioplasty in Oxford has coincided with an increase in the number of patients presenting with symptomatic aortoiliac occlusive disease and has allowed twice as many people to be treated while the number of aortobifemoral bypass operations has remained unchanged. It is concluded that the introduction of percutaneous transluminal angioplasty has not only generated its own workload but has also led to an increased demand for surgical reconstruction for aortoiliac occlusive disease.

Keywords: Aortoiliac occlusive disease, percutaneous transluminal angioplasty

In the past 35 years there have been several advances in the treatment of aortoiliac occlusive disease. Better surgical and anaesthetic techniques and better prostheses have contributed to an improvement in limb salvage and graft patency rates[1,2]. The development of less invasive techniques such as percutaneous transluminal angioplasty[3,4] and laser angioplasty[5] have increased the treatment options available.

The introduction and increased usage of percutaneous transluminal angioplasty might have been expected to reduce the need for major surgical intervention in the treatment of occlusive arterial disease. The purpose of this study was to discover what impact the introduction of this technique has made on the surgical treatment of patients with aortoiliac occlusive disease in Oxford.

Patients and methods

Between 1 January 1985 and 31 December 1988, 192 patients were treated for occlusive disease of the aorta or iliac arteries; there were 149 (78 per cent) men and 43 (22 per cent) women. The median age was 66 years (range 43–91 years). Treatment was classified as 'mandatory' if the patient had rest pain or critical ischaemia of one or both legs. Treatment was 'optional' in patients with intermittent claudication as their major symptom. The treatments carried out were aortobifemoral bypass, femorofemoral bypass, axillobifemoral bypass, aortoiliac endarterectomy and percutaneous transluminal angioplasty. All the data were obtained from the prospectively collected weekly audit of the vascular service.

Results

Between 1985 and 1988 the total number of patients treated for aortoiliac occlusive disease doubled. This increase coincided with major changes in the type of treatment carried out (*Figure 1*). Overall, 111 (58 per cent) patients were treated by an open surgical operation and 81 (42 per cent) were treated by angioplasty alone. In seven (6 per cent) of the surgical reconstructions peroperative percutaneous transluminal angioplasty was performed. Fifty-four (49 per cent) of the operations were aortobifemoral or aortoprofunda bypasses. The number of femorofemoral bypasses doubled from five to 12 per year but has remained as a constant proportion (16–20 per cent) of all cases treated. Between the first and last years of the study there was a 109 per cent increase in the number of patients treated for mandatory indications and an 85 per cent increase in those treated for optional indications (*Table 1*).

In 1985 only two percutaneous transluminal angioplasties were performed but in 1986 this number increased to 21 and in 1987 to 34. In the first 2 years of the study the use of percutaneous transluminal angioplasty was virtually confined to patients receiving optional treatment but in the last 2 years it was used to the same extent for patients in whom treatment was mandatory (*Table 1*). In 1985–86 only 9 per cent of patients requiring mandatory treatment had percutaneous transluminal angioplasty but in 1987–88 this proportion was 44 per cent.

The introduction of percutaneous transluminal angioplasty has significantly altered the proportion of patients treated for aortoiliac occlusive disease by aortobifemoral bypass or aortoiliac endarterectomy (*Figure 2*). In 1985, 61 per cent of patients were treated by aortoiliac surgery while in 1986 and 1987 this proportion had fallen to 18 per cent and 17 per cent respectively. In 1988 the total number of aortic operations had returned to the same level as in 1985 but accounted for only 32 per cent of all treatments given. Throughout the study period

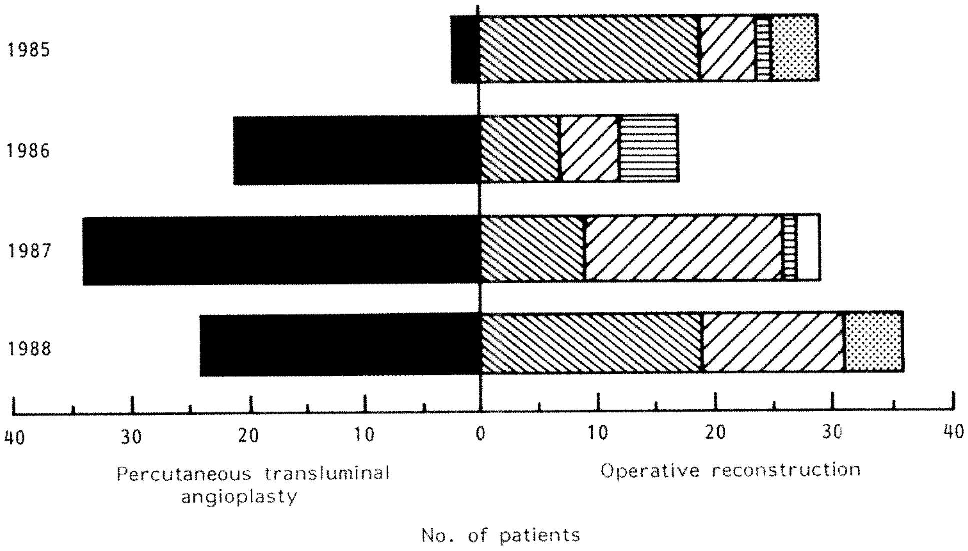

Figure 1 *Number of patients treated per year by the various techniques.* ▧, *Aortobifemoral bypass;* ▨, *femorofemoral bypass;* ■, *percutaneous transluminal angioplasty;* ☐, *endarterectomy;* ▤, *axillobifemoral bypass;* ▤, *femorofemoral and percutaneous transluminal angioplasty*

Table 1 *Number of patients treated per year for either 'mandatory' or 'optional' indications*

Year	No. of patients	Treatment mandatory	Treatment optional
1985	31	11 (1)	20 (1)
1986	38	11 (1)	27 (20)
1987	63	13 (8)	50 (26)
1988	60	23 (8)	37 (16)

Figures in parentheses are numbers of patients treated by percutaneous transluminal angioplasty

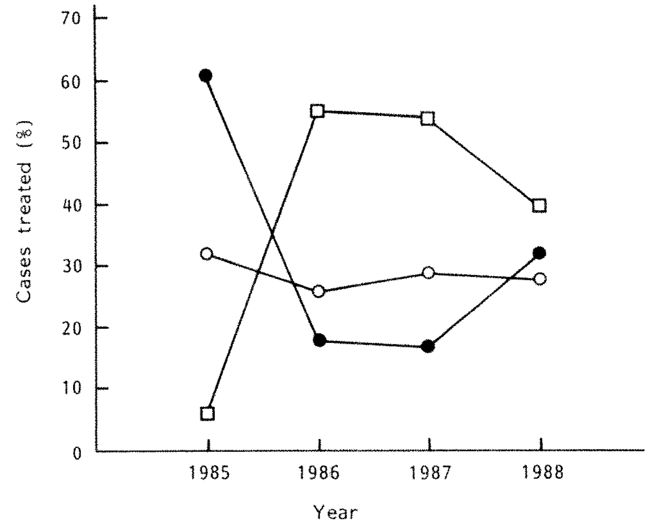

Figure 2 *Percentage of cases treated per year by the various techniques.* ☐, *percutaneous transluminal angioplasty;* ●, *aortobifemoral graft plus endarterectomy;* ○, *extra-anatomic, i.e. femorofemoral graft or axillobifemoral graft*

the proportion of patients treated by extra-anatomic bypass operations remained constant so that the total number of these operations almost doubled.

Discussion

The incidence of vascular disease has increased world-wide[1,6], with a consequent increase in vascular surgical workload[1,6–8]. In addition, greater awareness of the benefits which surgical treatment can offer has increased the number of patients with occlusive disease being referred for surgical assessment. Patients with aortoiliac occlusive disease may be treated by aortoiliac surgery, extra-anatomic bypass or percutaneous transluminal angioplasty. The indications for treatment are well established but controversy remains about which technique is best[9–11]. In the present series no strict guidelines were used to determine which treatment option was offered. The treatment given was that which was thought by the clinician at the time to be the most suitable.

Initially percutaneous transluminal angioplasty was used only in patients with optional indications for treatment but in the last years of the study it was used just as frequently for patients in whom treatment was mandatory. This change in practice reflects an early recognition that the success or failure of percutaneous transluminal angioplasty is not determined by the symptoms but by the anatomy of the arterial lesion. The slight fall in the proportion of patients treated with percutaneous transluminal angioplasty in the last year of the study and consequent resurgence of aortobifemoral bypass may represent a correction in practice as the limitations of percutaneous transluminal angioplasty were more clearly recognized, by both the surgeon and radiologist.

The use of percutaneous transluminal angioplasty in the treatment of aortoiliac occlusive disease has produced an improvement in the quality of surgical care. More patients than before are receiving the benefits of effective treatment and the proportion requiring the most major surgical intervention, aortobifemoral reconstruction, has been substantially reduced. As shown by others[12–15] the availability of percutaneous transluminal angioplasty widens the indications for angiography and increases by more than 50 per cent the number of patients successfully treated for chronic lower limb ischaemia[13]. In Oxford the introduction of percutaneous transluminal angioplasty, which is regarded as a minor procedure, appears to have stimulated the referral of many patients who were not being referred when major arterial surgery was perceived to be the only treatment option. The benefits of percutaneous transluminal angioplasty have therefore extended beyond those patients who are treated by it to those who would not have been exposed to other treatment options if percutaneous transluminal angioplasty had not been available. The cost and benefits of treatment by angioplasty have been well documented[16,17] but prospective randomized trials are needed to define the exact roles of angioplasty and surgery[18].

The use of extra-anatomic bypass which was initially devised for limb salvage[19–21] is now recognized as a valuable operation for the treatment of claudication. It has been shown that femorofemoral bypass is as effective as aortobifemoral bypass in the treatment of unilateral iliac artery disease[22,23]. Percutaneous transluminal angioplasty combined with femorofemoral bypass was described by Porter *et al.*[24] in 1973 and seven of the present patients were treated in this way.

It is concluded that the immediate consequence of the introduction of percutaneous transluminal angioplasty for aortoiliac occlusive disease was a substantial reduction in the number of surgical operations performed. This effect was short lived since the availability of percutaneous transluminal angioplasty seems to have stimulated an increase in both the number of patients referred and the proportion investigated by angiography. During the study period both conventional and digital subtraction angiography were available. In consequence the total number of surgical operations was greater in the fourth than the first year of the study. The eventual outcome of providing percutaneous transluminal angioplasty has been a doubling of workload for the vascular service and, contrary to expectation, an increased demand for operative surgical treatment.

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Conservative management of asymptomatic popliteal aneurysm

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Historical review shows that the treatment of popliteal aneurysm has developed by trial and error and there is disagreement about the proper management of the symptomless patient. In 1981 a policy of conservative management for asymptomatic popliteal aneurysm was adopted in this unit. Since that time we have also managed nine patients with thrombosed popliteal aneurysms by arteriography and low-dose intra-arterial streptokinase. Six patients treated within 72 h of occlusion achieved significant (70–100 per cent) lysis, but streptokinase was ineffective in those treated 10 or more days after the thrombosis. Of the six patients with significant lysis, three were treated by elective reconstruction and two by anticoagulation. One patient who had significant lysis died. Vascular patency of all five successfully treated limbs was maintained and no limb loss occurred in those who presented late and failed to achieve significant lysis. These results reinforce the view that thrombolysis is the treatment of choice for thrombosed popliteal aneurysms. The low complication rate for asymptomatic popliteal aneurysm and the advent of safe, effective thrombolysis indicate that operation for symptomless popliteal aneurysm is no longer required.

Keywords: Popliteal aneurysm, streptokinase, thrombolytic therapy, arterial thrombosis

Opposite views concerning the value of surgery for asymptomatic popliteal aneurysm have recently been expressed[1,2]. Many surgeons recognize that elective surgery for popliteal aneurysm is a low-risk procedure which may prevent serious complications. However, if thrombosis occurs the results of urgent surgery are poor, with limb loss in 36–69 per cent of cases[3,4]. Many surgeons therefore operate on symptomless popliteal aneurysms to prevent thrombosis. At its most extreme such a view may support operating on the symptomless aneurysm first, when a patient presents with bilateral disease but unilateral symptoms[4]. Recent analysis of outcome at one centre showed that patients harbouring symptomless popliteal aneurysms often remain symptomless unless they are treated surgically[2], and Bouhoutsos and Martin[4] have shown that the risk of limb loss with conventional surgery after thrombosis of a popliteal aneurysm depends on the patency of tibial vessels. Those presenting with popliteal aneurysm thrombosis and tibial vessel occlusion were shown to have a 69 per cent amputation rate within 3 years, but nearly two-thirds of those amputations were at the time of presentation. By contrast, those patients who had patent tibial vessels suffered an amputation rate of only 6 per cent at 6 years. It is clear that the failure of acute surgical intervention results from occlusion of distal vessels by either emboli or propagation clots and not from a fault in the bypass. Successful thrombolysis should improve outflow and outcome in these patients.

Since 1981 we have adopted the view that patients with asymptomatic popliteal aneurysms should be treated conservatively because, if thromboembolic complications occur, the limb may be saved by thrombolysis, which is now both relatively safe and effective[5]. This is a report of nine patients who presented with thromboembolic complications from popliteal aneurysms in whom this management has been followed.

Patients and methods

All patients presenting with acute ischaemia of the lower limb since 1981 were jointly assessed by a vascular surgeon and a radiologist for possible streptokinase therapy. Patients presenting within the first few hours of an occlusion and showing a 'white leg', characteristic of initial arterial spasm, were treated by conventional catheter embolectomy. No patient with popliteal artery thrombosis presented either in this way or with calf muscle necrosis requiring amputation. Patients were considered for streptokinase therapy regardless of the presumed duration of occlusion. They all underwent full diagnostic arteriography from the contralateral groin. A straight 5 Fr catheter with two side holes, approximately 1 cm from the tip, was embedded 1–2 cm into the obstructing thrombus. Streptokinase (Kabikinase®, KabiVitrum, Stockholm, Sweden) was infused at a rate of 6000 units/h for up to 48 h. A dose of 8000 units/h was given in one early case. The patients were nursed flat in the intensive care unit. Single-shot arteriography was carried out 6–14 h later, using non-ionic contrast medium. If there was lysis, the catheter was advanced; if there was no improvement, the infusion was continued but reassessment was delayed for a maximum of 12–14 h. At the end of treatment, a bolus of 1000 units of heparin was given through the infusion catheter and intra-arterial heparin was infused until withdrawal of the arterial catheter 4–5 h later. After removal, firm digital pressure was applied to the puncture site, sufficient to stop bleeding but not to occlude the vessel completely. Early elective surgery was then undertaken in fit patients, others being treated by anticoagulation.

Results

The results of treatment are shown in *Table 1*. Two patients presented with emboli from their popliteal aneurysms and four had a thrombosed aneurysm. These diagnoses were made clinically and confirmed arteriographically. Three further patients had thrombosed popliteal aneurysms, two of which were seen only after thrombolysis. Intra-arterial streptokinase infusion was attempted in all nine patients but was abandoned in one case because of failure to pass the catheter from either groin. This patient was treated with heparin alone followed by low-dose aspirin and the limb was saved. One patient had an approach from the ipsilateral groin because of failure on the contralateral side. There were therefore eight patients with thromboembolic complications from their popliteal aneurysms treated by low-dose intra-arterial streptokinase, seven of whom had rest pain and one claudication. They were all men aged 60–83 years (mean 74 years), and five had bilateral popliteal aneurysms. All six patients who were treated within 72 h of the occlusion achieved significant (70–100 per cent) lysis; no significant lysis occurred in the two patients treated ≥ 10 days after the occlusive episode. In those who achieved lysis, infusion times varied from 16 to 48 h with an average time of 32 h. There

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Table 1 *Results of low-dose intra-arterial streptokinase for acute thromboembolic complications of popliteal aneurysm*

Age (years)	Presentation	Arteriography	Infusion time (h)	Lysis (%)	Complications	Further treatment	Outcome
63	8 h rest pain Previous Dacron® graft for PA (7 years)	Thrombosed SFA above recurrent PA* above previous graft	48	90	Small groin haematoma	Resection aneurysm LSV graft Warfarin	Asymptomatic till death 5 years later from CVA
76	14 h rest pain Asymptomatic PA in the other leg Chronic renal failure	Occlusion of calf vessels by thrombus from PA	16	100	Small retroperitoneal haematoma	No surgery Warfarin Aspirin	Asymptomatic till death 5 years later
76	12 h rest pain	SFA occluded by thrombus*	23	70	Pelvic haematoma		Died of Mendelson's syndrome
60	48 h severe claudication	PA occluded by thrombus	24	100	None	Warfarin	Asymptomatic
44	2 years claudication 12 days rest pain Previously declined surgery	Bilateral PA occlusion	0	–	–	Heparin Aspirin	Asymptomatic
73	3 weeks rest pain Asymptomatic PA in the other leg	PA occluded by thrombus	14	0	None	Chemical sympathectomy Warfarin Amputation great toe	Asymptomatic
82	2 years claudication 10 days severe claudication Duodenal ulcer	SFA stenosis occluded distally by thrombus	17	0	None	Angioplasty before streptokinase infusion	Asymptomatic
78	10 h rest pain Asymptomatic PA other leg	PA occluded by thrombus with distal emboli	47	Pedal pulses palpable	Groin haematoma	Evacuation haematoma Reversed LSV graft Warfarin	Asymptomatic until death 1 month later after readmission with bronchopneumonia
83	60 h rest pain Bilateral PA with previous distal emboli warfarinized	PA occluded by thrombus	32	100 to pedal arch	None	PTFE graft Chemical sympathectomy Forefoot amputation	Healing foot ulcer 9 months later

CVA, cerebrovascular accident; PA, popliteal aneurysm; PTFE, polytetrafluoroethylene; SFA, superficial femoral artery; LSV, long saphenous vein
* PA revealed after thrombolysis by streptokinase

was no limb loss in either group although one patient needed a forefoot amputation and another required amputation of the great toe. One patient who had significant lysis died of Mendelson's syndrome after spontaneous intrapelvic haemorrhage and shock causing aspiration of vomit. This is the only directly related fatality in a series of more than 100 patients who have received thrombolytic therapy for acute lower limb ischaemia[5]. Of the five limbs which were salvaged, three were managed by elective reconstruction and two by anticoagulation; patency was maintained in all. The patient in whom it was not possible to pass the intra-arterial catheter was walking without pain 2 years later, having previously thrombosed his other popliteal aneurysm. In one patient who had had a Dacron® (E. I. du Pont de Nemours and Company, Wilmington, Delaware, USA) graft 7 years earlier for a popliteal aneurysm thrombosis, the delayed arteriograph revealed a further aneurysm proximal to the graft. This was treated by further bypass. Complications occurred in four of the patients. Two had minor haematomas, a third had a large haematoma requiring evacuation after pulling at the catheter himself, and the fourth patient died. None of these patients had a previously diagnosed asymptomatic popliteal aneurysm.

Discussion

Development of surgical treatment

The earliest recorded surgical treatment for popliteal aneurysm is attributed to Antyllus[6], a third century Greek, who ligated both poles of the aneurysm sac following which he opened and emptied it, leaving the wound to heal by secondary intention. Philagrius of Macedon, a century later, modified the technique by excising rather than opening the sac[7]. It was not until 1710 that Anel improved the method (in traumatic brachial aneurysms) by ligation of both poles of the sac but leaving the sac itself untouched[8]. This paved the way for Desault in 1785 to treat a spontaneous popliteal aneurysm similarly, although he ligated only the upper pole. Five months later, on the 12th of December, John Hunter operated on a 45-year-old coachman with a large, painful popliteal aneurysm. In contrast to his normal technique of ligation and emptying in the manner of Antyllus, he simply occluded the femoral artery above the aneurysm (in what was to be called Hunter's canal) by four loosely tied ligatures. The patient was described as being entirely well 6 months later and died 15 months after the operation from an unrelated cause. Hunter's rationale for proximal ligation has been attributed to his work on deer in which he ligated the carotid artery but found that growth in the ipsilateral antler resumed a few weeks later after the development of a collateral circulation. There is, however, no original report of this experiment and it seems more likely that he chose a proximal site for ligation to prevent the common and frequently lethal complication of secondary haemorrhage[8] as the coarse, unsterile ligatures sloughed out. The simplicity of this rapidly adopted procedure was offset by a significant incidence of distal gangrene, which according to Matas was 10·5 per cent[9]. Matas's own contribution in the latter half of the nineteenth century was endoaneurysmorrhaphy, treating the aneurysm by opening the sac, suturing the mouths of all the vessels entering it and suturing its walls together to obliterate the aneurysm without damaging any collateral vessels. This reduced the rate of distal gangrene to 5·2 per cent.

It was Pringle at Glasgow Royal Infirmary in 1912 who became the first surgeon in Britain to treat a popliteal aneurysm successfully by excision and restoration of continuity with a vein graft[10], but it was not until 1940, after Murray's introduction of heparin[11] for venous bypass grafting, that today's technique was widely used. In the intervening years surgeons employed a variety of techniques such as preliminary lumbar sympathectomy followed by aneurysmectomy. This was first successfully described by Bird[12] in 1935, and surgeons such as Linton[13], during the 1940s used it with surprising success: a single death and no amputation in 14 patients. He subsequently adopted saphenous vein bypass grafting a decade later.

Natural history of popliteal aneurysm

The popliteal artery is the most common site for the development of a peripheral atherosclerotic aneurysm[14]. Popliteal aneurysms are commoner in men (90–98 per cent) during the sixth and seventh decades. They are frequently bilateral (38–58 per cent), and are associated with hypertension (37–62 per cent), ischaemic heart disease (23–52 per cent), peptic ulceration (32 per cent), cerebrovascular disease and proximal aneurysms (32 per cent). The incidence of abdominal aortic aneurysms in patients with popliteal aneurysm doubles to 69 per cent if they are bilateral[4,15]. These patients have an increased mortality rate. In the series of Gifford *et al.*, 46 per cent of those diagnosed as having a popliteal aneurysm were dead within a mean time of 44 months[16]. This concurs with Vermilion *et al.*[3] who found a 50 per cent survival at 5·7 years compared with a 50 per cent survival of over 14 years in a matched general population.

The incidence of symptomatic popliteal aneurysm has been estimated at one admission per 5000 patient admissions, one popliteal aneurysm being seen for every 15 abdominal aortic aneurysms[17]. The incidence of asymptomatic popliteal aneurysm is difficult to ascertain, especially when one considers that the majority are diagnosed only when complications occur. The asymptomatic aneurysm is not always sought or detected on clinical examination. In the series of Downing *et al.* only 26 per cent of palpable, symptomatic popliteal aneurysms were diagnosed or even suspected in patients referred by their general practitioner to a vascular unit; in fact, 94 per cent were readily palpable[18]. The ratio of asymptomatic to symptomatic popliteal aneurysms seen in a vascular centre varies between 1:2 (References 3 and 16) and 1:1 (Reference 19). However, there is probably a much higher incidence of unidentified asymptomatic popliteal aneurysms in the general population.

The evolution of elective operation for the asymptomatic patient has been based on the high morbidity and mortality rate of complications of the aneurysm and a low operative risk. The most frequent complication is thromboembolism, with rupture occurring rarely (3 per cent)[3]. Little attention has been paid to the actual incidence of asymptomatic popliteal aneurysm and the rates of complications. In the 1940s Harley[20] and Linton[13] reviewed cases of popliteal aneurysm from Guy's Hospital and the Massachusetts General Hospital respectively, but neither report any of the aneurysms to be asymptomatic. Gifford *et al.*[16] reviewed 100 popliteal aneurysms seen at the Mayo Clinic between 1913 and 1951, of which 51 were uncomplicated, and of these 35 were asymptomatic. During a mean follow-up period of 46 months, 35 per cent of those conservatively treated uncomplicated popliteal aneurysms became complicated and almost all (85 per cent) resulted in above-knee amputation, but this was before the availability of catheter embolectomy or bypass grafting. They did not state whether the complications were in the symptomatic or the asymptomatic patients. In 1970 Wychulis *et al.*[19] reported the outcome in 87 uncomplicated popliteal aneurysms in asymptomatic extremities. Patients were followed for 1–8 years (mean 3·7 years) and 38 per cent remained asymptomatic. A further group harbouring 36 per cent of the aneurysms died 2 weeks to 7 years (mean 2·1 years) after the diagnosis. A total of 29 per cent became complicated leading to an overall amputation rate of 3 per cent. This compares very favourably with a group of 72 asymptomatic popliteal aneurysms reported by Reilly *et al.*[21] in 1983. These patients were treated with bypass grafting (Dacron or vein) and there were two postoperative amputations and seven graft occlusions. Schellack *et al.*[15] in 1987 reported the outcome of reconstructive surgery *versus* conservative management for 46 uncomplicated, asymptomatic popliteal aneurysms. Over half (26) were initially treated conservatively and almost all of these (92 per cent) were still symptom-free during a mean follow-up time of 37 months. Two patients developed complications requiring bypass grafting but there was no limb loss. Aneurysms treated by exclusion and bypass grafting (22) produced no further complicatons except in two patients who had graft thrombosis. Limbs were salvaged by thrombectomy and distal outflow angioplasty. In their series, Shellack *et al.* chose a conservative approach because of advanced age or concurrent symptomatic coronary and cerebrovascular disease, or because the patient declined surgery. The conservatively treated group was on average 12 years older. The results concur with the work of Hands *et al.*[2] where all five asymptomatic popliteal aneurysms treated conservatively were still symptomless 4–8 years later, whereas only four (57 per cent) treated by ligation and bypass grafting were still asymptomatic 1–2 years later.

Role of thrombolysis in the management of thrombosis and embolism

The use of streptokinase for the treatment of thrombosis in the popliteal artery is not new, being first described in 1962 by Cotton *et al.*[22] following a partially successful femoral embolectomy. They used a loading dose of 50 000 units of streptokinase via an intra-arterial catheter followed by a further 56 000 units over the next 5 h to produce radiological clearance to the foot. The first successful use of low-dose intra-arterial streptokinase for thrombosis of a popliteal aneurysm was reported in 1984 by Schwarz *et al.*[23], with lysis of the clot in the aneurysm and outflow tracts being followed by successful bypass grafting the next day. Since then Ferguson *et al.* have treated 23 thrombosed popliteal aneurysms by thrombolysis. Three of their patients required amputation but, of the remainder, 18 were treated by subsequent surgical bypass and two by thrombolysis and anticoagulation, all with limb salvage[24,25]. All seven of their originally treated patients had viable limbs after 6–24 months. We have treated eight patients with popliteal artery thromboses by initial thrombolysis and achieved a satisfactory distal patency in six. Two patients failed to achieve significant lysis but both presented 10 days after the presumed thrombosis. These results are in keeping with previously published results[23–25], suggesting that initial low-dose intra-arterial streptokinase significantly improves the results of surgery for thromboembolic complications of popliteal artery aneurysms.

We would suggest that initial management of choice for thromboembolic complications of popliteal artery aneurysms is arteriography and low-dose intra-arterial streptokinase. It allows identification of the pathology which is often not evident (70 per cent) in the series of Ferguson *et al.*[24] and may also show other vascular lesions. It may thereby prevent an inappropriate thrombectomy which, even when combined with bypass grafting, has an amputation rate of >50 per cent[4]. Clearance of the tibial vessels by thrombolysis overcomes the major obstacle to successful bypass surgery in those patients who develop thromboembolic complications of their popliteal aneurysm. This means that bypass surgery need only be offered to those patients with a symptomatic aneurysm and not as a precaution to all those who are symptomless. Aneurysm size has not been included in the present data for two reasons: firstly because Inahara and Toledo[26] showed that thromboembolic complicatons of popliteal aneurysm were not related to the size of the aneurysmal sac, and secondly because of the difficulties associated with measurement of the aneurysm, namely tortuosity of the lumen and the uncertainty as to which parameter to measure. A very large popliteal aneurysm is unlikely to be asymptomatic but in these patients we would offer surgical repair, especially if there had been a recent increase in size.

It is important to remember that patients with popliteal aneurysm are unlikely to develop complications from their aneurysms as long as they are symptomless. We have no doubt that complicated or symptomatic popliteal aneurysms should be treated by early operative repair, but the low reported complication rate leads us to suggest that asymptomatic popliteal aneurysm is best treated conservatively in those centres where safe thrombolysis is available. Further experience comparing elective repair with this conservative approach may finally allow us to reassure our patients that an asymptomatic popliteal aneurysm does not carry the risk of limb loss.

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Acute limb ischaemia: the place of intravenous streptokinase

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Intravenous streptokinase infusions (100 000 units/h) have been used to treat 48 patients, with 50 episodes of acute limb ischaemia who were unlikely to benefit from a surgical approach. These included 17 acute thromboses, 14 late or distal emboli and 19 bypass graft occlusions. Overall, 17 (34 per cent) instances had complete lysis with reappearance of distal pulses and a further 28 per cent had clinical improvement without change in pulse status. Final outcome after 30 days was limb salvage in 60 per cent, amputation in 24 per cent and death in 16 per cent, but this was achieved after eight patients without lysis had vascular reconstructive surgery. Serious complications were infrequent, but included a fatal stroke, a haematemesis and two episodes of distal embolization. The outcome was not related to the duration of ischaemia or the site of occlusion. Lysis was more frequent with emboli (50 per cent) and graft occlusions (47 per cent) than arterial thromboses (6 per cent). Limb salvage was more likely in patients with no neurological deficit in the limb (70 per cent) than if a deficit was present (37 per cent). In conclusion, intravenous streptokinase produced a moderate benefit with low morbidity and has a role in acute limb ischaemia if surgery is inappropriate and intra-arterial lysis unavailable. In particular, selected patients with emboli or graft occlusions without a neurological deficit may be most suitable.

Keywords: Thromboembolism, fibrinolysis, streptokinase

Since Tillett and Garner[1] observed the fibrinolytic activity of proteases produced by streptococci in 1933, the search has continued for safe, effective, methods of achieving *in situ* thrombus dissolution with pharmacological agents. In the 1960s intravenous streptokinase was given to patients with acute limb ischaemia with only limited success and a worrying number of haemorrhagic complications[2–4]. Since Dotter *et al.* described regional fibrinolysis using one-twentieth the concentration of streptokinase given through an indwelling arterial catheter[5], the technique has been shown to be effective with relatively fewer bleeding complications[6,7]. Low-dose intra-arterial streptokinase is an accepted alternative to surgery in the management of selected cases of acute limb ischaemia[8,9]. However, the Dotter technique is time consuming, and requires fairly advanced radiological skills and equipment, and close cooperation between surgeons and radiologists, which may be difficult to organize, particularly out of hours[9]. This method of thrombolytic treatment for acute limb ischaemia has certainly not been uniformly accepted by surgeons.

Intravenous infusions of streptokinase have been widely recommended in the treatment of acute myocardial infarction combining the advantages of efficacy with ease of administration. Despite a paucity of recent data, a survey in 1989 documented that one-third of UK vascular surgeons experienced with thrombolysis had used intravenous streptokinase for acute peripheral arterial ischaemia in the previous 12 months[10]. Intravenous streptokinase infusions are used in Plymouth to treat selected patients with acute limb ischaemia. Experience with the technique in 48 patients has been reviewed retrospectively to try to identify its role in the management of this difficult condition.

Patients and methods

The study included 48 patients with 50 episodes of acute limb ischaemia; there were one upper limb and 49 lower limb occlusions. There were 19 women and 29 men, of median age 68 years (range 31–90 years). Seven patients (15 per cent) had diabetes mellitus and 18 (38 per cent) admitted to regular cigarette smoking. All patients had ischaemic pain at rest. The median duration of ischaemic symptoms was 6 days (range 1–56 days). A total of 13 episodes (26 per cent) had symptoms for less than 24 h, and 28 (56 per cent) for less than 1 week. Sixteen (32 per cent) episodes had signs of a limb neurological deficit on admission and 49 per cent of those assessed had no audible Doppler ankle artery blood flow.

These patients represented a small proportion of those presenting to a vascular unit in a busy district general hospital over a 5 year period. Thrombolytic treatment was selected for the patients if the likelihood of a good result from urgent thromboembolectomy or reconstructive vascular surgery was in doubt. In particular 17 episodes of acute-on-chronic arterial thromboses were selected for thrombolysis because of either advanced age and infirmity of the patient or poor state of the distal vessels. Fourteen episodes of either distal or delayed presentation emboli (range 3–28 days) were thought suitable for thombolysis, along with 19 episodes of acute thrombosis of a bypass graft (*Table 1*).

The patients were given a detailed examination on admission,

Table 1 *Clinical details*

	No. of cases	Percentage
Site of 50 occlusions		
Iliac	13	26
Femoral	29	58
Popliteal	3	6
Brachial	1	2
Bilateral	4	8
both iliacs	2	
both tibials	1	
one popliteal, one femoral	1	
Cause of 50 occlusions		
Native vessel thrombosis	17	34
Embolism	14	28
Graft thrombosis	19	38
femoropopliteal	12	
aortofemoral	6	
iliofemoral	1	

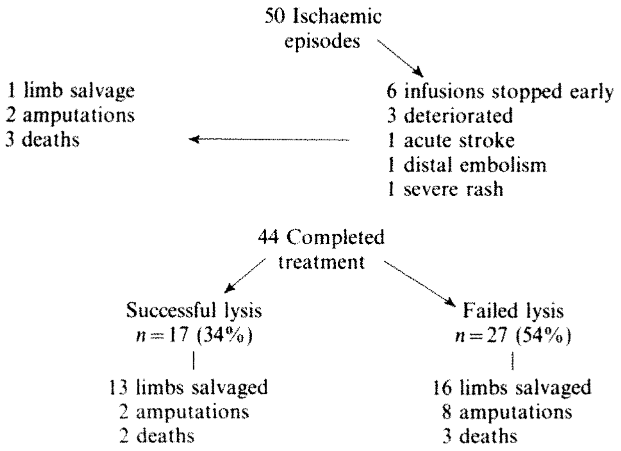

Figure 1 *Results of intravenous streptokinase for acute limb ischaemia with 30 day outcome*

Table 2 *Further procedures after failed thrombolysis*

	Total	Limb salvage
Femoropopliteal bypass	3	3
Aorto/iliofemoral bypass	4	2
Thromboembolectomy	1	0
Sympathectomy	1	1

including documentation of pulses and ankle pressures. On 40 occasions a decision was made at this time that surgery was inappropriate and primary treatment with streptokinase was commenced. Angiography was not performed, to minimize the risk of local haemorrhage. The other ten patients had arteriographs which demonstrated occlusions unsuitable for surgery and these subsequently received thrombolysis between 1 and 10 days later.

Thrombolysis was commenced after an intravenous injection of 100 mg hydrocortisone to prevent allergic reactions. A loading dose of streptokinase was then infused intravenously over 1 h to overcome any circulating streptococcal antibodies. The most frequent loading dose given was 250000 units, but during the study period it varied from 100000 to 650000 units. Subsequently an infusion of 100000 units/h streptokinase was given for 3 days.

The patients were monitored on a ward where the nurses were used to caring for vascular patients. Hourly observations were recorded throughout the treatment and the patients were closely watched for signs of haemorrhage, particularly at any puncture sites. Coagulation tests and blood counts were measured daily. The ischaemic limb and the pulse state were also carefully observed. The infusion was stopped if there were any complications or if distal pulses reappeared. If there was no change in the ischaemic limb after 72 h, it was not usual to continue streptokinase treatment.

After the streptokinase was stopped, heparin was given to patients with successful lysis, defined as restoration of distal pulses. The heparin was subsequently changed to warfarin and continued for life. If the limb remained painful after streptokinase treatment, it was reassessed and, unless irreversibly ischaemic, angiography was performed followed by vascular reconstruction, if appropriate. After 30 days, or at hospital discharge if sooner, the patients were classified into categories of limb salvage, amputation or death. The patients were subsequently followed up regularly in the outpatient department.

Results

Intravenous streptokinase produced lysis of occluding thrombus with restoration of distal pulses in 17 (34 per cent) instances. Fourteen (28 per cent) limbs improved clinically without objective evidence of change in pulses, 14 (28 per cent) were unaltered and five (10 per cent) deteriorated on treatment. After 30 days (or hospital discharge if sooner) salvage was achieved for 30 (60 per cent) patients, 12 (24 per cent) required amputation and eight (16 per cent) patients died.

Withdrawals

Six patients failed to complete a course of intravenous streptokinase (*Figure 1*). In three cases the ischaemic limb deteriorated during therapy; two patients died from the effects of continued ischaemia, and one limb was saved by successful vascular reconstruction. One further patient suffered a dense stroke and died 5 days later. Another patient with an iliac thrombosis developed distal embolization during treatment and subsequently required bilateral amputation. One patient having a second course of streptokinase, 2 years after the first, developed a severe skin rash.

Successful lysis

A total of 17 (34 per cent) patients had successful lysis with reappearance of distal pulses. After 30 days, 13 remained well. Two patients required amputation following early rethrombosis, 48 h and 96 h respectively after the streptokinase infusion ended. Two patients died, one from a ruptured aortic aneurysm 17 days later while on warfarin, and one 3 days after treatment from unrelieved distal ischaemia despite successful restoration of flow in an occluded aortobifemoral graft. No additional procedures were performed in this group.

Follow-up of this group revealed that all but one of the patients is alive a median of 13 months later (range 4 months to 5 years). Three patients had a late rethrombosis. Two of these necessitated vascular reconstructions, of which one was unsuccessful and ended in amputation.

Failed lysis

Distal pulses were not restored in the remaining 27 patients who completed a 72 h course of streptokinase without event. In this group limb salvage was achieved by 16 patients, five after vascular reconstructions and one after sympathectomy. Eight patients required amputation, three after failed vascular reconstructions. Three patients died, two from the effects of unrelieved ischaemia with bronchopneumonia, and one from an acute myocardial infarction. In the series overall, eight patients had vascular reconstruction after failed thrombolysis, limb salvage being achieved in five cases (*Table 2*).

Follow-up of the 16 patients with limb salvage after failed thrombolysis revealed that all are still alive a median of 15 months later (range 7 months to 5 years). In the follow-up period four patients had further reconstructive surgery and four patients had late amputation. Three patients had troublesome claudication and one a leg ulcer which healed only slowly.

Serious complications with intravenous streptokinase were infrequent (*Table 3*) but included a fatal stroke, two episodes of significant distal embolization (one which resulted in bilateral amputations) and a haematemesis which responded to conservative therapy.

Successful lysis was much more likely for emboli (50 per cent) and graft occlusions (47 per cent) than thromboses (6 per cent). However, limb salvage rates for emboli (57 per cent), graft occlusions (73 per cent) and thromboses (47 per cent) were not significantly different. Lysis rates were better for occluded grafts positioned above the inguinal ligament (57 per cent) compared with those below (42 per cent),

Table 3 *Complications of intravenous streptokinase*

Complication	No. of cases
Major	
Distal embolization	2 (1 amputation)
Acute stroke (died)	1
Haematemesis	1
Minor	
Haematoma	6 (12%)
Heart failure	3 (6%)
Pyrexia	3 (6%)
After second course of streptokinase (2 patients)	
Severe rash	1
Severe phlebitis	1

but the numbers were small and the limb salvage rates similar in each group. The site of the native vessel occlusion bore no relation to outcome, nor did the duration of the arterial ischaemia. Lysis rates were similar whether a limb neurological deficit was present (35 per cent) or absent (31 per cent). However, limb salvage was significantly reduced in patients with a neurological deficit (37 per cent) compared to those without (70 per cent).

Discussion

Initial enthusiasm with intravenous streptokinase in acute limb ischaemia was tempered by a relatively low lysis rate of around 30 per cent and a major complication rate of 10–15 per cent[2–4]. This study reviews the use of streptokinase in three specific groups of patients known to have a poor outcome from conventional surgical techniques, namely those with acute-on-chronic thromboses, those with distal and late presenting emboli and those with graft thrombosis[11,12]. The overall lysis rate of 34 per cent accords with previous publications. Although clinically acceptable lysis rates were achieved for emboli (50 per cent) and graft occlusions (47 per cent), the dissolution rate of 6 per cent for thromboses was disappointing. Limb salvage rates were similar in all groups, but were obtained only after extensive salvage reconstructive surgery in patients with thromboses.

Lysis rates have previously been reported to be best for emboli[2,4], although there have been warnings about the possibility of further embolization caused by the treatment[3]. This has not been confirmed by clinical experience, although distal embolization of a lysing thrombus can occasionally be a serious problem. Several authors have also identified graft occlusions as favourable for intravenous streptokinase[13,14], although the numbers were small and other reports were not confirmatory[15]. Adjunctive surgery has been stated to be required frequently after thrombolysis of graft occlusions[15], but in the present series long-term anticoagulation alone was sufficient for prolonged patency in most patients. The severity of the ischaemia at presentation was confirmed as a significant predictor of outcome in this study[2], but the duration of ischaemia did not appear to be as crucial as others have suggested[3].

The major complication rate from thrombolysis was low, although one patient died from a stroke and one required amputations after distal embolization. This rate is lower than previously reported, possibly because of exclusion of patients at high risk of haemorrhage[16] and avoidance of diagnostic angiography in most patients, which reduced the risk of bleeding from arterial puncture sites. A non-invasive assessment seems ideal for these patients. A small risk of serious haemorrhage is unavoidable in thrombolytic treatment and it is unlikely that the present rate can be reduced[17].

One possibility of improving the results of intravenous thrombolysis is to use new fibrin-specific agents. These agents have an affinity for fibrin which may increase dissolution of the occluding thrombus. Their specificity may also reduce the degradation of plasma fibrinogen which occurs with streptokinase therapy and is the main cause of haemorrhagic complications. Anistreplase (Eminase®, Beecham Pharmaceuticals, Brentford, UK) is an acylated complex of plasminogen and streptokinase which results in prolonged fibrinolytic activity. Anistreplase can be given as a single intravenous bolus for acute myocardial infarction. However, when a smaller dose (5 mg, equivalent to 180000 units streptokinase) was given 8 hourly over 3 days to patients with acute peripheral arterial occlusions, the clinical results were no better than those reported with intravenous streptokinse, and haemorrhagic complications were frequent[18,19]. Tissue plasminogen activator (t-PA) (Actilyse®, Boehringer Ingelheim, Bracknell, UK) is a naturally occurring fibrinolytic agent produced by recombinant DNA technology in sufficient quantities for clinical use. Exceptional results have been reported with intra-arterial t-PA for acute limb ischaemia[20] and, in a randomized trial, lysis rates with intra-arterial t-PA (100 per cent) were far superior to those recorded with intravenous t-PA (45 per cent)[21]. Lastly, the intermittent use of high doses of intravenous streptokinase, or 'burst therapy', has been shown to allow plasma fibrinogen time to recover between injections, but has not yet been shown to have any advantage over continuous infusions[22].

Randomized comparison of intravenous streptokinase and low-dose intra-arterial streptokinase have yet to be performed in similar patients. However, in a randomized study, lysis with intra-arterial streptokinase (80 per cent) was superior to that with intravenous t-PA (45 per cent)[21]. Combined with information from the large number of open studies that intra-arterial streptokinase produces lysis in about two-thirds of patients treated[6,7], it is reasonable to state that the latter is presently the thrombolytic method of choice in acute limb ischaemia.

It is the opinion of several recent reviewers that thrombolytic therapy is a real alternative to surgery in selected cases of acute limb ischaemia[8,9], and that low-dose intra-arterial streptokinase is currently the gold standard against which other agents should be tested[23]. Early results have suggested that t-PA may replace streptokinase as the agent of choice[24].

However, there is still a role for intravenous streptokinase in selected cases, particularly if the intra-arterial route is impossible for technical reasons, or not available. In particular, patients with distal and late presenting emboli and those with graft occlusions may be most suitable, especially if there is no limb neurological deficit. In the long run the ideal method of treatment of these specific groups of patients will require a randomized comparison.

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Short note

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Dynamic angioplasty of total arterial occlusions

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Percutaneous transluminal balloon angioplasty is an effective technique for the treatment of arterial stenosis and short occlusions. However, when used for long and chronic total occlusions it has a relatively high failure and complication rate[1]. Alternative techniques including a variety of laser and mechanical devices are developing rapidly[1]. This is a report of the use of a percutaneous dynamic angioplasty device – the Kensey catheter (Theratec and Cordis, Miami, Florida, USA).

Patients and methods

Twenty men, aged 54–74 years, with history of disabling intermittent claudication were included. Median claudication distance was 30 yards, range 0–70 yards; two patients had pain at rest. Mean duration of symptons was 2·5 years. Angiography demonstrated total occlusion in 3 iliac and 17 femoral arteries (3–16 cm, mean = 10 cm). In all patients, an attempt to cross the occlusions with a steerable guide wire failed. Percutaneous dynamic angioplasty was carried out under local anaesthesia using an 8 Fr (2·7 mm) Kensey catheter (*Figure 1*) at a cam speed of 40 000–80 000 revolutions per minute. The technique was approved by the ethical committee and informed consent was obtained from all patients. When successful, the procedure was followed by balloon dilatation of the recanalized segment.

In addition to clinical follow-up, ankle/brachial Doppler pressure index (ABPI) and hyperaemia-induced limb blood flow (LBF) using ^{99}Tc-labelled albumin[2] were measured before recanalization and at 3 weeks, 3 months and 6 months after each procedure. Long-term patency was assessed by re-angiography 9–12 months after recanalization. All patients received 75 mg aspirin (daily) and 100 mg dipyridamol (three times a day) starting one day before the procedure and continuing until re-angiography. All results are expressed as mean(s.e.m.). The paired Student t test was used to assess the significance of changes in ABPI and LBF.

Results

In all patients it was possible to reach the lesion with a steerable guide wire. However, this failed to cross the occlusion. Dynamic angioplasty using the Kensey catheter successfully recanalized the whole length of the occlusion in 15 patients (*Figure 2*). In three patients, only part of the occluded segment was recanalized; in this group complete recanalization was prevented by dissection in two cases and by perforation in one. In the remaining two patients early perforation precluded any recanalization. There was no correlation between the length of the occlusion and the result of dynamic angioplasty.

In the 15 lesions that were successfully recanalized, a small dissection was observed angiographically in three (*Figure 2b*) and contrast extravasation was observed in two. In one patient early reocclusion (within a few hours) necessitated repeat balloon angioplasty which was associated with thrombotic embolism. However, no atheromatous embolism was observed during the use of the Kensey catheter.

Full recanalization resulted in symptomatic improvement in all 15 patients. There was a significant improvement in ABPI and LBF (*Table 1*). Some symptomatic improvement was also felt by two of the three patients in whom recanalization was incomplete. No worsening of claudication was experienced in those two patients with primary failure. There was no fall in ABPI or LBF in patients who had no or incomplete recanalization (*Table 1*).

Re-angiography was performed in 10 of 15 patients who had full recanalization. Patency was demonstrated in eight.

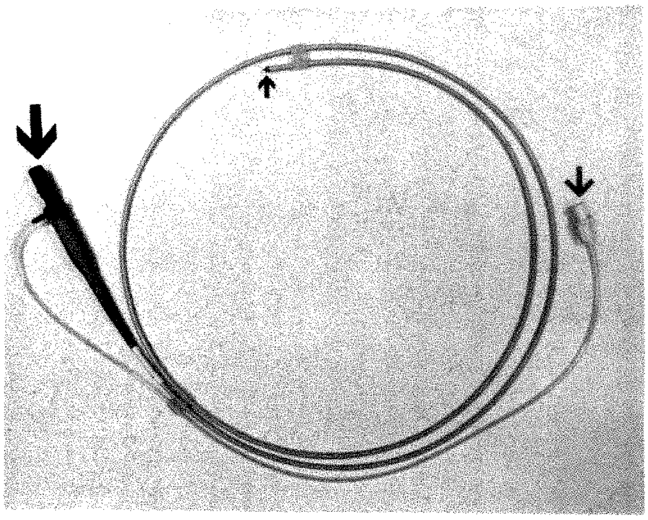

Figure 1 *The Kensey catheter: rotating cam at the tip (middle arrow); connection to motor (left arrow); flushing port (right arrow)*

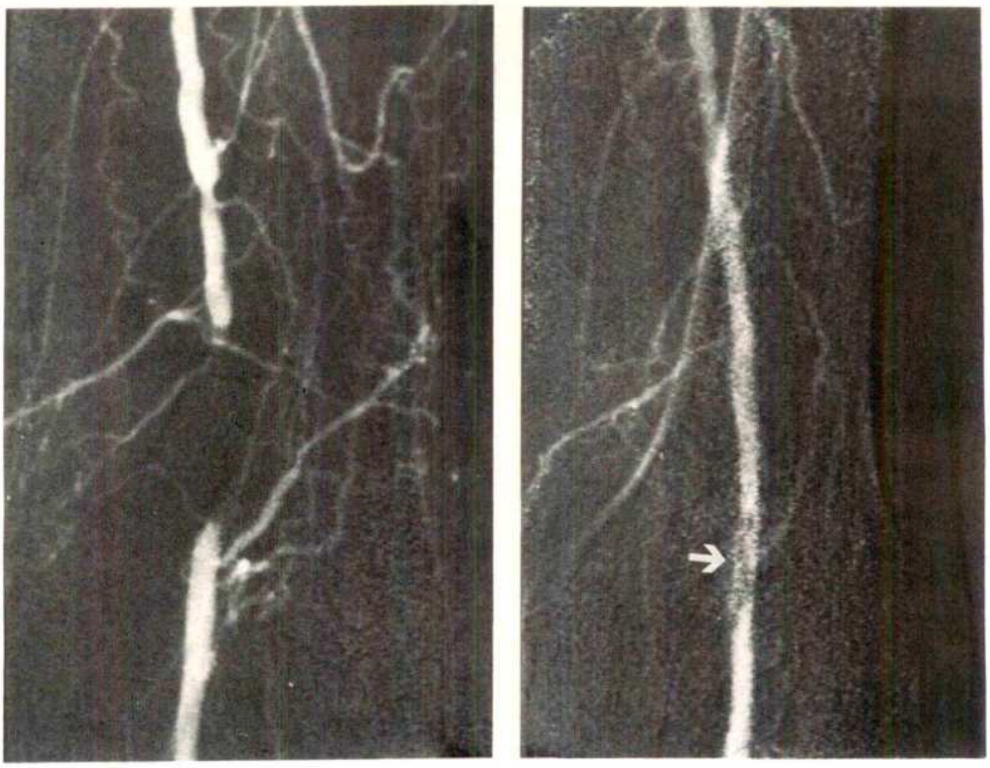

Figure 2 **a** *Angiogram showing total superficial femoral artery occlusion;* **b** *this was recanalized using dynamic angioplasty which was associated with a dissection (arrow)*

Table 1 *Ankle/brachial Doppler index (ABPI) and limb blood flow (LBF) in 20 patients who underwent dynamic angioplasty for symptomatic chronic arterial occlusions. While successful recanalization significantly improved ABPI and LBF* **a**, *neither index was worsened following unsuccessful procedures* **b**. *Results are mean(s.e.m.). Normal LBF> 10 ml/100 ml tissue/min*

a	Complete recanalization ($n=15$)	
	ABPI	LBS (ml/100 ml tissue/min)
Preangioplasty	0·56(0·04)	4·4(0·4)
Postangioplasty	0·62(0·04)	
3 weeks later	0·85(0·05) $P<0{\cdot}001$	9·4(0·8) $P<0{\cdot}001$
3 months later	0·80(0·04) $P<0{\cdot}001$	8·2(0·9) $P<0{\cdot}01$)
b	Incomplete or no recanalization ($n=5$)	
Preangioplasty	0·58(0·04)	3·6(0·4)
Postangioplasty	0·60(0·04)	
3 weeks later	0·65(0·03)	4·0(0·5)
3 months later	0·55(0·04)	3·9(0·4)

One patient developed an asymptomatic popliteal artery aneurysm.

Discussion

Balloon angioplasty is an established technique for non-operative treatment of stenotic arterial disease. In chronic total occlusions, however, persistent attempts to cross the lesions with a guide wire are often associated with complications[1]. Restenosis is another major limitation which often necessitates repeat dilatation. Several laser and dynamic angioplasty techniques to overcome these problems are under investigation. It is hoped that actual atherectomy by these devices, rather than splitting of the atheroma by balloon angioplasty, will increase the primary success rate in chronic occlusions and reduce the restenosis rate[1].

In this article, we report on the first series of patients treated by dynamic angioplasty in the UK. In all 20 patients the total occlusions demonstrated angiographically were associated with disabling symptoms. Although the mean duration of symptoms was 2·5 years, this is not necessarily the duration of the occlusions. While angiography alone is an insensitive means of detecting the composition of the occlusive pathology[3], failure to cross these lesions with the guide wire strongly suggests a chronic and atheromatous nature. While long occlusions reduce the success of the wire technique, it is difficult to foresee the outcome in any individual lesion. In the present series, guide wire passage was considered not to be feasible only after a reasonable attempt.

Some operators have successfully used the Kensey catheter to recanalize lesions up to 40 cm long and for lesions in femoropopliteal bypass grafts[3]. Our primary success rate of 75 per cent is comparable with unpublished multicentre results of 77 per cent in 110 patients. As a limb salvage technique, Wholey *et al.* used the Kensey catheter to treat six patients with pregangrenous extremities; amputation was avoided in three[4].

Direct comparison of the present results with those using other atherectomy devices is difficult since most of the latter incorporate a guide wire in their structure and are predominantly used in stenotic lesions. Wholey *et al.* used a transluminal extraction catheter in 95 patients and reported a success rate of 92 per cent; however only 16 patients had total occlusions. Twelve of these 16 were recanalized by a transluminal extraction catheter (Interventional Technologies, Inc., San Diego, California, USA) which is led by a guide wire[4]; the present patient group is more comparable with the remaining four patients. In a similar study using the Simpson catheter (AtheroCath Devices for Vascular Intervention, Inc., Redwood City, California, USA), Hofling *et al.* treated 41 patients; only five had 100 per cent total occlusions[5].

Although embolism of atheromatous debris is a potential hazard of dynamic angioplasty[6], this was not observed in the present series. However, subclinical embolic episodes cannot be excluded since sizeable particles have been observed in experimental studies[7]. Smaller particles were reported with the Rotablator (Squibb Inc., USA), another on-the-wire atherectomy device[8]. Angioscopy has also shown that it produces a smoother lumen than the Kensey catheter. Simpson and transluminal extraction catheters retrieve excised atheroma; however, the risk of embolism is not eliminated[9]. The atheroma retrieved from recurrent lesions re-treated by the Simpson catheter have provided an important insight into the possible mechanism of restenosis[9].

The technique of LBF was originally described by Parkin *et al.*[2]. Recently, its value in the assessment of laser and dynamic angioplasty has been reported[10]. Following successful recanalization, both ABPI and LBF continue to improve over the first 3 weeks. This is probably due to remodelling of the treated segments. When recanalization was incomplete, the symptomatic improvement may be related to the opening of some collaterals in the recanalized portion. Failed dynamic angioplasty does not seem to worsen symptoms or compromise LBF.

Successful recanalization was always followed by balloon dilatation; therefore the final result does not represent the effect of atherectomy alone. In an experimental study, Demopulos *et al.* showed that dynamic angioplasty was associated with a significantly larger chronic lumen (less restenosis) than balloon angioplasty in similar lesions[11]. No clinical studies have addressed this question. Re-angiography was done 9–12 months after angioplasty which assessed patency at a longer interval than in most other studies. Finally, initial attempts to cross the lesions with a guide wire may have contributed to dissections seen in some lesions subsequently recanalized by a Kensey catheter; however, long-term complications were rare[12].

In conclusion, the limited data presented suggest that dynamic angioplasty is an effective technique for percutaneous recanalization of occluded arteries. Even when lesions were only partially recanalized, there was some symptomatic improvement. LBF was not compromised following unsuccessful procedures. Further studies would be necessary before the final place of this technique in the treatment of vascular disease is established.

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Trauma centres and the efficient use of financial resources

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The economic aspects of trauma centres were examined using published results and local financial data to discover if such institutions are an efficient use of resources. The cost of trauma centre care depends upon the number of centres built. An 'ideal' system in the UK of eight centres will cost £31 268 per life saved compared with £45 661 for the system proposed by the Royal College of Surgeons of England. Trauma centre care will be expensive but will generate benefits in return. Survivors will be young (mean age 30 years) and most (70–80 per cent) will regain their pre-injury functional/work status. When considered in terms of Quality Adjusted Life Years (QUALYs), trauma centres are a relatively efficient use of resources. An expected cost per QUALY of £942–1376 is inexpensive compared with many health pursuits currently funded within the UK National Health Service.

Keywords: Trauma centres, cost benefit analysis

Each year more than half the deaths resulting from severe trauma in the UK occur after admission to hospital. There is evidence that many of these could be avoided if the care of such individuals was concentrated in trauma centres[1–3]. This conclusion led the Royal College of Surgeons of England (RCSE) to recommend the creation of a trauma centre network resembling those in parts of Europe and the USA[3]. To date no such centre exists in the UK and some doubt surrounds their value. It is incontrovertible that trauma centres save lives but this may not justify their existence. The cost of trauma centres and the quality of life experienced by those who survive must be considered. This paper explores these questions to determine if such institutions are an efficient use of resources.

How many additional lives would be saved by trauma centre care?

In the UK each year 14 500 people die as a result of trauma and at least half die after admission to hospital[3,4]. The RCSE concluded that 30 per cent of these deaths could be avoided if severely injured patients were managed in Trauma Centres, thus saving 2175 lives each year[3].

How long will survivors remain in hospital and what is their expected quality of life thereafter?

Consideration of the outcome of trauma centre care is inevitably based on experience reported from the USA where penetrating injuries occur more commonly than in the UK. This makes extrapolation of results difficult and conclusions unreliable. However, some centres[5–7] have studied patient populations similar to those in the UK in terms of the cause (55–83 per cent blunt trauma, mostly or exclusively road traffic accidents) and severity of injury suffered (Injury Severity Score 28·1–49·1). Their results show a close measure of agreement with each other and allow certain conclusions to be made about the outcome of future trauma centre care in this country.

Survivors will spend approximately 28 days in hospital, 50 per cent of which is in intensive care. On discharge from hospital, 20 per cent of survivors have regained their pre-injury functional status. Others require longer periods of rehabilitation, the length of which is determined by the area(s) injured, social, educational and economic factors. One year after injury, 80 per cent of survivors are independently mobile and able to undertake selfcare without assistance. Fifty-seven per cent of those who worked before injury will have returned to their previous employment. Two and a half years after injury, 78 per cent of those severely injured (Injury Severity Score > 15) will be judged to have achieved a good outcome with no disability or expressing the capacity to resume normal occupational and social activities despite minor physical or mental deficits. Seventy per cent will have regained their former work status and more will return to work eventually.

Up to 10 per cent of survivors are severely disabled, requiring some assistance with activities of daily living ranging from total dependence to needing help with only one major activity. Very few (1–2 per cent) survive in a vegetative state and these die within the first year after injury. The remainder, approximately 10 per cent, are moderately or 'independently' disabled, being unable to undertake some previous activities by reason of either physical or mental deficit.

Methods

How much will the system cost?

The purpose of this study is to illustrate the potential cost of trauma centres. It is recognized that other changes were recommended by the RCSE which could also affect the cost of trauma management in this country[3]. Of note in this respect are prehospital care and transportation. Additional expenditure may be incurred but the level of extra spending is difficult to estimate and is unlikely to be substantial. The National Health Service is already committed to funding a more highly skilled ambulance service and the RCSE did not suggest alterations to the type of emergency transport used. In particular, increased use of helicopters (which would be very costly) was not recommended[3].

In calculating the cost of trauma centres, it is assumed that the cost of caring for those whose outcome is not altered by these institutions is the same as if they were treated in an ordinary hospital. The cost is therefore the additional expenditure incurred by the National Health Service in caring for those who 'unexpectedly' survive (i.e. avoidable hospital deaths under present conditions) and in providing the environment which allows this. *Table 1* shows cost calculations for an 'ideal' system of eight centres in the UK and that proposed by the RCSE with one centre per two million people, i.e. a network of 25 centres. 'Ideal' trauma centres admit 1000 severely injured patients each year[8] and eight would be required to treat the 7250 individuals who currently die from the effects of severe trauma after hospital admission.

The revenue cost of patient care is calculated using data from the Regional Neurosurgery Unit in Oxford[9] where each inpatient day (intensive care unit at £1500 per day and ward at £250 per day) includes the cost of care undertaken by junior

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Table 1 *Cost of Trauma Centres*

	'Ideal' system (8 centres)	RCSE (25 centres)
Lives saved per centre (total = 2175 per year)	272	87
Cost of hospital stay per patient (14 days ITU at £1500, 14 days ward at £250)*	£24 500	£24 500
Total cost of patient stay per year	£6 664 000	£2 131 500
Cost		
Consultant	£365 000	£365 000
Theatre	£476 000	£476 000
Capital	£1 000 000	£1 000 000
Total cost per centre	£8 505 000	£3 972 500
Cost per life saved	£31 268	£45 661

* Includes junior medical time, nursing, drugs, investigations and ancillary facilities. ITU, intensive care unit

Table 2 *Quality of life valuation matrix*[10]

Disability rating	Distress rating			
	A	B	C	D
I	1·000	0·995	0·990	0·967
II	0·990	0·986	0·973	0·932
III	0·980	0·972	0·956	0·912
IV	0·964	0·956	0·942	0·870
V	0·946	0·935	0·900	0·700
VI	0·875	0·845	0·680	0·000
VII	0·677	0·564	0·000	−1·486
VIII	−1·028	–	–	–

1, year of full health; 0, death; —, not applicable

hospital doctors (not consultants), nursing, drugs, investigations and ancillary facilities. To this must be added the cost of continuous 'in-house' consultant expertise in five specialties defined by the RCSE (general surgery, accident and emergency, anaesthesia, intensive care and orthopaedic surgery)[3]. If average consultant remuneration is £100 per day (24 hours) and each day working in a trauma centre counts as two (the second is spent resting), then the cost of consultant care is £1000 per day or £365 000 per year. The cost of providing a continuous operating theatre facility is also added to the revenue expenditure.

The capital cost of building and commissioning each trauma centre is divided over 10 years which is the probable 'life-time' of much of the plant and equipment installed[8]. The yearly capital expenditure of £1 000 000 is expected to continue, allowing for replacement as necessary. In certain situations it may be possible to upgrade or alter existing facilities. While this would be less expensive, it is difficult to predict where and when this will be possible. For the sake of simplicity, these calculations assume that all trauma centres will be established *de novo* and illustrate the most expensive scenario.

Is this an efficient use of financial resources?

To compare the benefits of trauma centre care with those generated by other health pursuits, it is necessary to quantify the change in life expectancy produced and adjust it for effects on quality of life. Benefit is measured in terms of Quality Adjusted Life Years (QUALYs) and the economic efficiency of health activities compared in terms of the expenditure required on each pursuit to produce a single QUALY. The most desirable and cost efficient QUALYs are those which are least expensive.

Two principal components of quality of life[9] have been defined as disability (physical mobility) and distress (freedom from pain). Kind *et al.*[10] classified disability as follows: I, no disability; II, slight social disability; III, severe social disability or slight impairment of performance at work/home, or both; IV, choice of or performance at work severely limited/light housework only; V, unable to undertake paid employment, continue education or shop, a few single tasks possible in the house; VI, confined to chair or wheelchair or able to move only with support; VII; confined to bed; and VIII, unconscious. Four levels of distress are recognized: A, none; B, mild; C, moderate; and D, severe.

Combinations of the classifications I–VIII and A–D can describe all health states valued between zero (death) and one (a year of normal health). *Table 2* shows the valuation elicited for each state of health from 70 respondents[9]. Some severe states are regarded as worse than death and are given a negative valuation. A valuation of 0·5 implies that an individual's quality of life for a given year is half that enjoyed by someone fit and well.

Those achieving a good functional recovery after trauma centre care (78 per cent of survivors) would have a QUALY score of at least 0·9 and those making a moderate recovery (10 per cent of survivors) would score at least 0·7. Judging those who fair less well is difficult and it is assumed that they all (12 per cent of survivors) score zero, i.e. only the benefits enjoyed by 88 per cent of survivors are considered.

Table 3 outlines the calculation of the total number of QUALYs generated by each trauma centre and their cost. *Table 4* is a summary of the cost and benefits of some other health pursuits for comparison[11].

Discussion

Trauma centres will be expensive. Depending on the number, the system will cost between £68 million and £100 million per year to run and the cost of saving each life between £31 000 and £46 000. These amounts are at the upper limit or exceed the equitable sum available within the Health Service. In 1981–82, when total National Health Service expenditure was £11·5 billion, £14 000 was available to all to save life or prevent serious disability without reducing the potential benefit to others[12]. Spending on the health service is now £26 billion, implying that the present equitable sum is £31 700. Clearly cost

Table 3 *Expected number and value of Quality Adjusted Life Years gained from trauma centres*

	Cost per centre per year	QUALYs gained per centre per year*	Cost per QUALY
'Ideal' system (272 survivors per centre year)	£8 505 000	9029	£942
RCSE system (87 survivors per centre per year)	£3 972 500	2887	£1376

* 78 per cent good outcome, QUALY score ⩾0·9; 10 per cent moderate outcome, QUALY score ⩾0·7; life expectancy = 43 years (from Life Tables, Office of Population Censuses and Surveys, 1987)

Table 4 *Summary of cost and benefits of some selected treatments*

Treatment	Value of extra service costs (£)	Value of extra service costs per QUALY gained (£)
Kidney transplant (cadaver)	15 000	3 000
Haemodialysis		
In hospital	70 000	14 000
At home	66 000	11 000
Coronary artery bypass graft (3 vessels)	2 850	1 270

must be taken into account when a decision is made concerning the number of trauma centres to be established. A system as near to the 'ideal' as possible is desirable and would be equitable but it may be necessary to violate the principal of equity to establish a realistic working network. This may not be unreasonable when the benefits of such an action are considered.

Survivors of trauma centre care are young and most achieve a good quality of life, regain their previous work/functional status and enjoy a life expectancy equal to that of an uninjured subject of the same age. A considerable financial gain accrues from trauma centre care, generated by those who return to work and who remain in the work-force until retirement age. Their earnings offset the cost of the centres and counterbalance the on-going cost of caring for those who remain dependent after injury.

Trauma centres also produce less tangible benefits. They will probably reduce avoidable complications as well as avoidable death, minimizing the cost of hospital stay and preventing long-term sequelae. They should provide a 'centre of excellence' for teaching and research. The centralization of major injury victims may increase the rate of organ donation for transplantation.

The economic assessment of health care in terms of the number and cost of the QUALYs produced is a currently accepted method of cost-efficiency analysis which should improve collective health if properly applied[10,11]. Trauma centres produce a large number of QUALYs which, although expensive, are cheaper than those generated by many presently funded activities which also violate the principal of equity in terms of their total required expenditure. Judged by these criteria, trauma centres represent an efficient use of resources and would be funded preferentially if strict economic policies were applied. They should have a place in a health service which considers 'quality' and 'efficiency' as keywords for the future[13].

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On-table pancreatography: importance in planning operative strategy

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We describe our experience with 124 on-table pancreatograms performed during 117 operative procedures on 112 patients in a wide variety of clinical settings. Endoscopic retrograde cholangiopancreatography (ERCP) was performed on 84 occasions with a 73 per cent success rate for visualization of the main pancreatic duct. On-table pancreatography (OTP) was performed by one of five different techniques: retrograde, prograde or ambigrade ductography, cystography and ascending loopography after pancreaticojejunostomy. OTP provided important information about the main pancreatic duct when endoscopic visualization was unsuccessful (n = *23*), *incomplete* (n = *17*) *or not performed* (n = *33*)*; there was a failure rate of 4 per cent. In 35 patients either the additional information or discrepancies between ERCP and OTP findings resulted in a change of operative plan (19 extra procedures, 16 altered procedures). Complete ductography was especially helpful in the 63 patients with chronic pancreatitis. OTP is technically simple, free from complications and invaluable for planning operative strategy.*

Keywords: On-table pancreatography, operative adjunct, chronic pancreatitis, pancreas divisum

Complete demonstration of the pancreatic ductal tree is important, not only for the diagnosis of pancreatic disease but also for planning the best operative treatment, particularly in chronic pancreatitis. Preoperative imaging of the main pancreatic duct (MPD) is possible by means of endoscopic retrograde cholangiopancreatography (ERCP), ultrasonography, computed tomography (CT)[1–4], CT scanning after ERCP[5] and more recently by ultrasound-guided percutaneous opacification of the pancreatic duct[6,7]. Each technique has the drawback that ductal imaging may be unsuccessful, inadequate or actually misleading.

On-table pancreatography (OTP) offers the surgeon a full definition of pancreatic ductal anatomy without serious risk of pancreatitis since injection pressures are low. Likewise, pseudocysts can be outlined with particular reference to their extent and ductal communication. A personal experience of 124 on-table pancreatograms is reported.

Patients and methods

One hundred and twelve patients treated at the Bristol Royal Infirmary and Hammersmith Hospital underwent 117 operative procedures, during which 124 OTPs were performed. There were 68 male and 44 female patients, ranging in age from 8 years to 79 years (median 48 years). Preoperative imaging of the pancreas included ultrasonography ($n=62$), computed tomography ($n=71$), visceral angiography ($n=30$) and ERCP ($n=84$). ERCP was not undertaken in 33 patients, comprising 14 with pseudocysts, six with painful chronic pancreatitis who had other imaging, nine with obstructive jaundice (who had percutaneous cholangiography), three with obscure pain and one with gastric outlet obstruction.

OTP was undertaken by one of five routes:

Retrograde ductography – via a transduodenal approach to the major papilla or accessory papilla or via the duct in the neck of pancreas after a proximal resection (*Figure 1*). The transduodenal approach is utilized during sphincteroplasty if preoperative imaging is inadequate.

Prograde ductography – via the duct in the neck or body of the pancreas after a distal resection, to delineate the duct in the head of the pancreas and confirm free flow of contrast to the duodenum (case 1 below).

Ambigrade ductography – via a scalp vein needle introduced directly into a dilated MPD in the neck or body of pancreas (*Figure 2*), as a prelude to pancreaticojejunostomy.

Cystography – via a needle or Foley catheter inserted into a pseudocyst (*Figure 3*) to determine its size, extent and ductal communication; up to 100 ml of contrast may be instilled after aspiration of cyst contents.

Loopography – this technique was employed in one patient with a previous pancreaticojejunostomy (case 3 below). The Roux loop was clamped just distal to the anastomosis, and contrast material was inserted into the jejunum above this point via a needle.

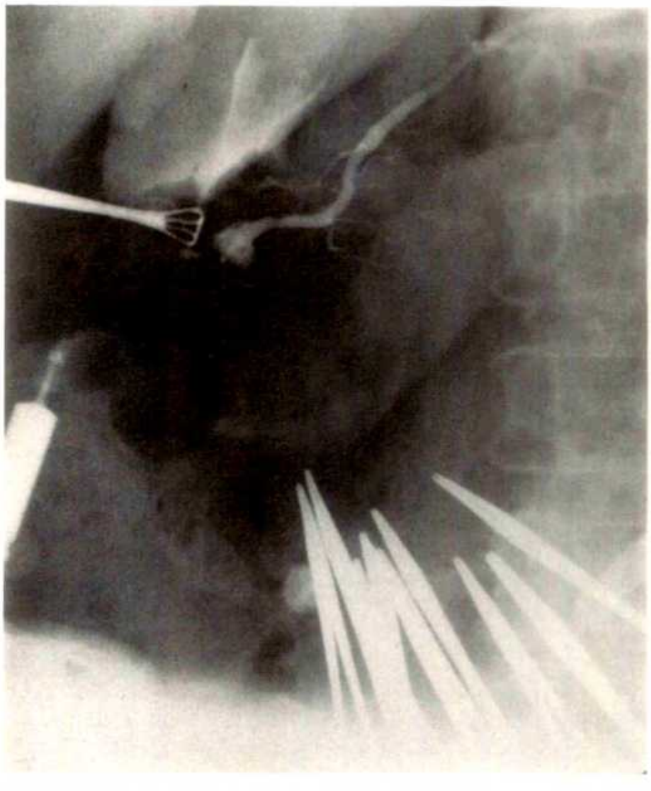

Figure 1 *Retrograde operative pancreatogram via the accessory papilla, in a patient with pancreas divisum. The dorsal pancreatic (Santorini) duct is opacified*

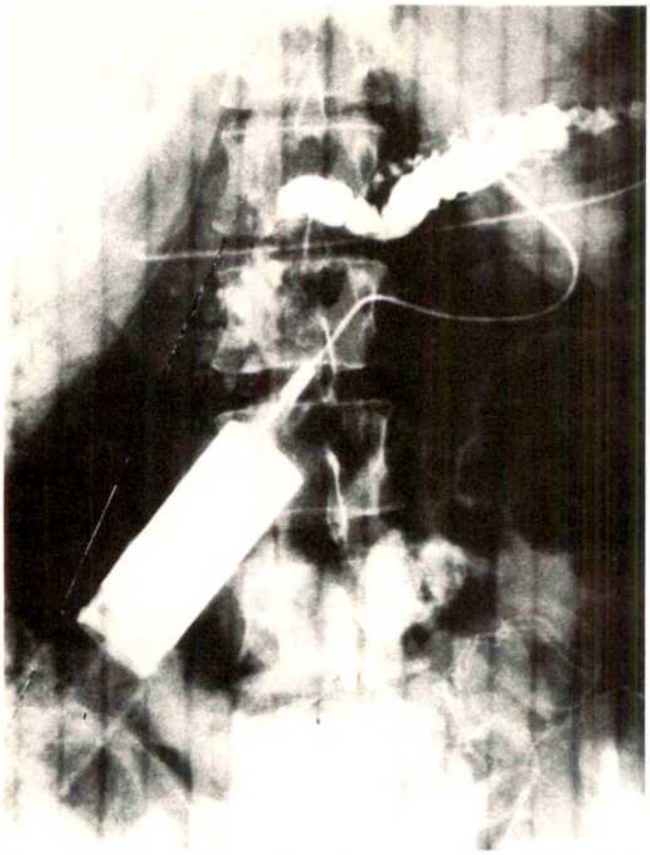

Figure 2 *Ambigrade pancreatogram in a patient with chronic pancreatitis. (The vertical striations in the background are due to a water bed.) The need for operative pancreatography had not been anticipated in this patient in whom ERCP had indicated a complete ductal stricture in the neck of pancreas*

Details of most of these techniques were given in a previous communication[8], but retrograde ductography from the neck and 'loopography' were not described. Although Hypaque (Sterling Research UK, Guildford, UK) was used in the earlier part of the series, we now prefer to use Omnipaque (Iohexol-Nycomed AS, Birmimgham, UK) which gives a denser ductogram. An image intensifier is used during the procedure. Retrograde ductography from the papilla is 'covered' with an intravenous injection of aprotinin (Trasylol, Bayer UK Ltd., Newbury, UK, 1×10^6 units) to prevent postoperative pancreatitis.

Results

Clinical material (Table 1)

There were 63 patients with chronic pancreatitis, six with pseudocysts following acute pancreatitis and 13 with recurrent acute pancreatitis. The 14 pancreas divisum patients presented with either obscure abdominal pain ($n=9$) or recurrent acute pancreatitis ($n=5$). Six of the eight patients with post-cholecystectomy pain had undergone an evocative morphine-prostigmine (Nardi) test[9] with positive results. Papillary fibrosis was suspected in several patients with obscure abdominal pain and clearly documented in three. The five patients with irresectable pancreatic cancer had ambigrade ductography to confirm an ectactic duct suitable for intubated pancreatico-gastrostomy to relieve pain[10].

ERCP

There was an 83 per cent success rate for cannulation of at least one duct at ERCP (70/84 investigations), though the main pancreatic duct (MPD) was only visualized in 73 per cent of cases (61/84 investigations). The ductal changes on endoscopic pancreatography (ERP) were classified according to Axon and co-workers[11]. Pancreas divisum was diagnosed in 14 patients, but accessory duct cannulation was never achieved. Thirty patients had complete visualization of the MPD, with normal ($n=10$), dilated ($n=11$) or strictured ($n=9$) ducts. Seventeen patients had incomplete vizualisation, with obstruction due to stricture ($n=11$) or concretions ($n=6$). Post-injection pancreatitis developed in three patients (4 per cent).

OTP (Table 2)

OTP was attempted on 124 occasions. There were five technical

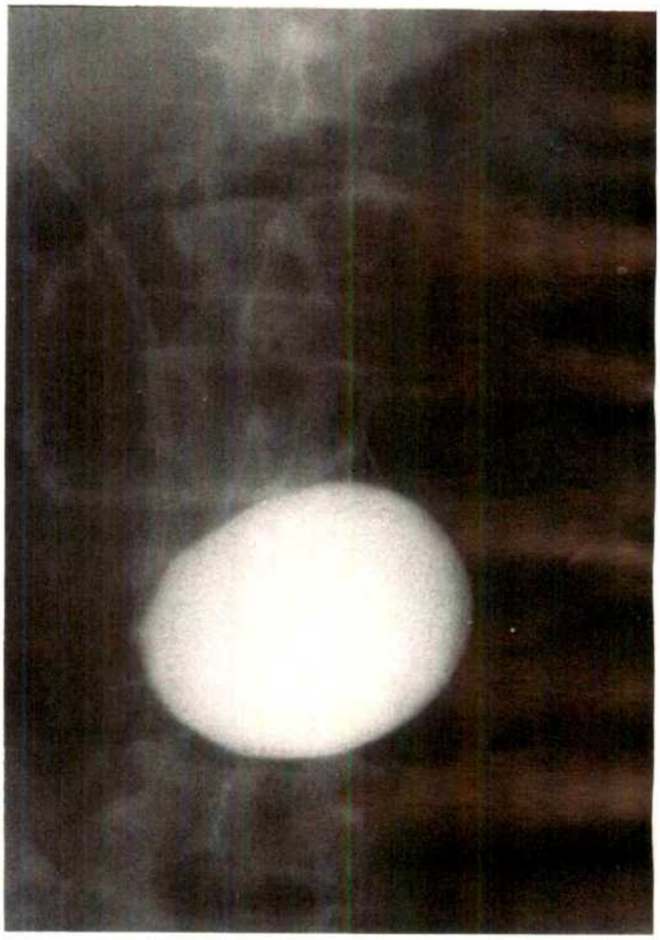

Figure 3 *Pancreatic cystogram in a patient with jaundice and pseudocysts complicating chronic pancreatitis. There is no ductal communication. The endoprosthesis inserted for biliary decompression is clearly visible*

Table 1 *Indications for operation and number of endoscopic retrograde cholangiopancreatograms (ERCPs) attempted*

Indication	No. operative procedures	ERCP
Chronic pancreatitis		
Pain*	44	38
Cysts	12	4
Jaundice	9	6
Acute pancreatitis with pseudocysts	6	–
Recurrent acute pancreatitis	13	13
Obscure abdominal pain		
Post cholecystectomy	8	7
Pancreas divisum	9	9
Papillary fibrosis	3	–
Other†	8	6
Carcinoma of pancreas	5	1
Total	117	84

* One patient had three operations for pain of chronic pancreatitis; † one patient had three and another had two laparotomies for obscure pain

Table 2 *On-table pancreatography (OTP) findings*

			Duct calibre			Duct communication	
	n	Failed	Normal	Dilated	Stricture	No	Yes
Ductogram							
Prograde	33	1	24	7	1		
Retrograde							
From major papilla	32	3	21	7	1		
From accessory papilla	4	–	4	–	–		
From neck of pancreas	13	1	7	4	1		
Ambigrade	20	–	1	19	–		
Loopogram	1						1
Cystogram	21	–	–	–	–	16	5

Table 3 *Correlation between endoscopic retrograde cholangiopancreatography (ERCP) and on-table pancreatography (OTP)*

ERP		OTP					
			Duct calibre			Duct communication	
	n	Failed	Normal	Dilated	Stricture	No	Yes
Complete visualization MPD	30						
Normal		1	9	–	–	–	–
Dilatation		–	3	8	–		
Stricture		1	1	6	–	1	–
Obstructed MPD	17						
Concretion		1	2	3	–	–	–
Stricture		–	3	1	–	2	1
Pancreas divisum	14	–	14	–	–	–	–
Failed ERP	23	1	12*	9	–	1	–

MPD, main pancreatic duct. * This includes the patient with pancreas divisum who had an unsuccessful ERCP

failures (4 per cent) owing to a tiny duct (in two cases), a tight stricture, an obstructing stone or extravasation of contrast through the major papilla. The total number of successful ductograms (98) included 45 retrograde examinations, 32 prograde, 20 ambigrade and one ascending loopogram. Ductal dilatation was shown in 37 examinations but stricture in only three. Pancreatic pseudocysts communicated with the MPD in five of 21 cases (24 per cent).

Correlation between ERCP and OTP (Table 3)

In only 17 of the 30 cases with complete visualization of the MPD on ERP were matching appearances obtained on OTP. Among the remaining 13, seven patients thought to have a stricture on ERCP had normal (1) or dilated (6) ducts and three with 'dilated' ducts on ERCP actually had normal ducts. In three patients OTP was not obtained, twice because of technical failure and once because cystography was performed instead.

There were 17 patients with obstruction of the MPD on ERCP. OTP demonstrated previously unseen ducts in the tail in eight, but a stone prevented on-table cannulation in the ninth; three had cystograms to look for ductal communication, one had a prograde pancreatogram to rule out a pancreas divisum, and four proceeded straight to distal pancreatectomy. In all 14 patients with pancreas divisum, OTP revealed normal Santorini ductal systems (there being no endoscopic dorsal pancreatogram). OTP was particularly helpful in 22 of the 23 patients with failed endoscopic visualization of the MPD. It showed normal ducts in 12, ectatic ducts in nine and ductal communication by means of a cystogram in one case. It was also useful in 32 of the 33 patients in whom ERCP was not attempted.

The additional information gained by OTP when MPD visualization was not attempted ($n=32$), unsuccessful ($n=22$) or incomplete ($n=12$), together with a lack of concordance between ERP and OTP findings, resulted in an operative change in plan in 35 patients. Nineteen patients had additional procedures and sixteen patients had altered procedures.

Additional operative procedures (Table 4)

In six patients undergoing a proximal pylorus-preserving pancreatectomy, retrograde ductography from the neck of the pancreas revealed unexpected dilatation in the body and tail. The duct was therefore incised along the remaining (distal) pancreas to allow side-to-side pancreaticojejunostomy rather than the routine end-to-end anastomosis. Among four patients scheduled for distal pancreatectomy alone, OTP led to additional proximal resection (i.e. total pancreatectomy) in one and drainage of a dilated duct in the head in the other three. An illustrative example is given.

Case 1. A 42-year-old man developed acute-on-chronic pancreatitis with a small pseudocyst and resolving pancreatic ascites. ERCP showed a ductal ectasia without overt stricture (*Figure 4a*). Following 70 per cent distal pancreatectomy, a prograde pancreatogram revealed an unsuspected stricture behind the ampulla allowing only a trickle of contrast to enter the duodenum (*Figure 4b*). A proximal pancreaticojejunostomy was therefore added to the distal resection.

Five patients undergoing cystjejunostomy had additional ductal drainage into the same Roux loop as a consequence of OTP. Four of these five had ductal communication on cystography, one communication being particularly narrow. The fifth patient is described below.

Case 2. A 68-year-old man presented with obstructive jaundice from chronic pancreatitis. CT scan showed a large multilocular cyst displacing the superior mesenteric vessels, but ERCP failed to opacify the pancreatic duct. Cyst drainage alone was planned. At laparotomy the MPD was turgid, and an

Table 4 *Additional or alternative procedures undertaken as a consequence of the findings of on-table pancreatography*

		Additional procedures		Altered procedures		
Operation planned	*n*	Resection	Drainage	Resection	Drainage	Laparotomy alone
Proximal pancreatectomy	19	–	6	1	4	1
Distal pancreatectomy	33	1	3	1	3	–
Total pancreatectomy	1	–	–	–	–	–
Cystjejunostomy	19	–	5	2	–	–
Longitudinal pancreaticojejunostomy	13	–	–	4	–	–
Sphincteroplasty	26	4	–	–	–	–
Other	6	–	–	–	–	–
Total	117	5	14	8	7	1

ambigrade pancreatogram revealed gross ectasia. Longitudinal pancreaticojejunostomy was performed in addition to the cystjejunostomy, with complete symptomatic relief.

Four patients undergoing sphincteroplasties had distal pancreatectomy as well. Two were carried out for unsuspected evidence of a narrow, irregular duct in the tail. One of these resection specimens was histologically normal, the duct probably being underfilled with contrast during the pancreatogram (false positive result). In the other two ductal stricturing in the neck necessitated prograde pancreatectomy for complete evaluation.

Altered operative procedures (Table 4)

Six patients scheduled for proximal pylorus-preserving pancreatectomy ended up having totally different procedures as a result of OTP. One had a distal pancreatectomy. One was thought to have a carcinoma of the head of pancreas on ERCP and CT scan but had a normal pancreas on palpation and a normal retrograde OTP. Three with failed ERCP had sphincteroplasty instead of proximal pylorus-preserving pancreatectomy. In two of these CT suggested a diseased head of pancreas but OTP was normal. The third had calcification of the head of pancreas on CT, but OTP revealed pancreas divisum; accessory pancreatic sphincteroplasty was therefore performed. The final patient had disease localized to the head on CT scanning but ambigrade ductography revealed gross ectasia; longitudinal pancreaticojejunostomy was carried out instead.

Of four patients scheduled for distal pancreatectomy, one had proximal pylorus-preserving pancreatectomy while the other three had drainage procedures. One of the cases is described below.

Case 3. A 25-year-old woman had undergone longitudinal pancreaticojejunostomy five years earlier for recurrent attacks of acute pancreatitis associated with a dilated MPD. Further recent attacks led to repeat ERCP, which now showed an obstructing stricture in the head of pancreas and no communication with the bowel (*Figure 5a*). A distal resection was planned. However, an operative loopogram showed free communication between jejunum and distal duct (only) (*Figure 5b*). Pancreatic sphincteroplasty was therefore performed to drain the proximal duct, with a good result 2 years later.

Two patients due to undergo cystjejunostomy for drainage of cysts in relation to the body and tail did not have preoperative imaging of the MPD (ERCP unsuccessful). At laparotomy, the distal pancreas was extensively diseased on OTP, so distal pancreatectomy was performed to include the cysts. Three patients thought to have dilated MPDs were found to have relatively small ducts (4 mm diameter) on OTP, so longitudinal pancreaticojejunostomy was abandoned in favour of partial pancreatectomy. In a similar case described below, the extent of disease necessitated total pancreatectomy.

Case 4. A 31-year-old man presented with pain of alcoholic chronic pancreatitis. ERCP suggested moderate dilatation of the MPD, and CT scan showed calcification in the body and tail. Longitudinal pancreaticojejunostomy was planned, but the gland was grossly diseased and shrunken at laparotomy and an ambigrade OTP revealed minimal ductal dilatation (4 mm diameter). Total pancreatectomy was performed instead.

Discussion

Originally popularized by Doubilet[12] in the 1950s, OTP was the only method of visualizing the pancreatic duct before the advent of ERCP, and it became a standard operative manoeuvre[5,13–15]. During the last two decades the successive emergence of other imaging modalities for the pancreas has rather diminished the importance attached to OTP. We believe that OTP remains an essential part of the surgical armamentarium, particularly in managing conditions such as chronic pancreatitis, pancreas divisum and pseudocyst, in which complete ductography is desirable but can be elusive. The results of the present study support this contention: in 56 patients ERCP was not attempted or pancreatic duct cannulation was not achieved, and in another ten the appearances were frankly misleading.

Among 124 OTPs obtained during 117 operative procedures, there were five technical failures and one false positive result because of underfilling of the pancreatic duct. The technique of OTP is simple and free from complications. Only one of our pancreatograms showed parenchymal extravasation, though several patients with sphincteroplasty had transient postoperative elevation of serum amylase. The injection of aprotinin may have had some bearing on the absence of clinical acute pancreatitis, but the low injection pressure used to obtain the radiograph was probably contributory.

Among pancreatic imaging modalities ERP is particularly valuable for delineating ductal anatomy, though it exaggerates ductal diameter when compared to ultrasound[16]. Percutaneous pancreatography under ultrasound control is not readily available in many centres; success rates of 89 per cent have been reported[6,7]. The technique requires no special equipment and can be quick and easy to perform, but only if the main pancreatic duct is dilated[7].

Pitfalls in endoscopic pancreatography result from technical errors, anatomic variation and conditions that mimic pancreas divisum[17]. Our overall cannulation rate (83 per cent) is within the published range (75–90 per cent)[4,18,19], but our rate for visualization of the MPD (73 per cent) is poorer than those of Gilinsky *et al.*[3] (93 per cent) and Bornman *et al.*[2] (83 per cent). Since experienced endoscopists were involved and the incidence

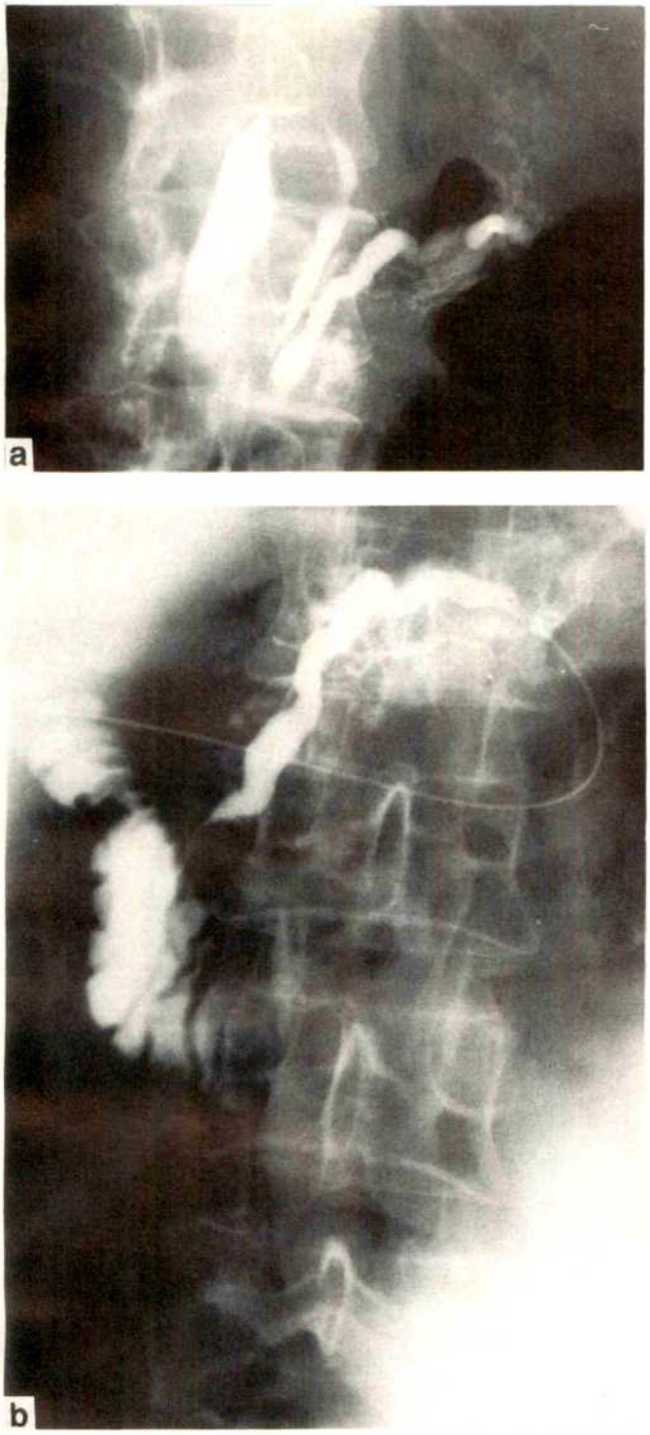

Figure 4 *Chronic pancreatitis (case 1).* **a** *ERCP shows ductal ectasia without overt stricture. Following distal pancreatectomy a prograde pancreatogram* **b** *shows an unsuspected stricture immediately behind the ampulla, which allows only a trickle of contrast to enter the duodenum. Drainage of the proximal duct was therefore added*

of unsuccessful ERCP has not diminished with time, the failure rate probably reflects the pathology in this series. Patients requiring operation for severe chronic pancreatitis often have inflammation and distortion of the duodenum. Underfilling of the duct can also lead to misinterpretation[17]. In our series seven patients with ductal 'strictures' on ERCP had normal or dilated ducts on OTP, while three 'dilated' ducts were normal. Gautier-Benoit[20] recommends OTP in all patients with chronic pancreatitis, even those with successful ERCP.

In chronic pancreatitis the surgical objective is to relieve pain without impairing function. Although stricture and ectasia of the duct are not always the cause of pain[2], longitudinal pancreaticojejunostomy is safer than pancreatic resection, and the results are superior provided the MPD is dilated (>8 mm diameter)[21]. Initial pain relief and long-term patency of the anastomosis depend upon the presence of a dilated duct[18,22–24]. Since ERCP is unreliable at showing ductal ectasia, the surgeon must examine the pancreas fully at operation and insert a needle into a dilated duct that may be palpable behind the 'stricture' in the head or neck.

Pancreatic pseudocysts only communicated with the main pancreatic duct in 24 per cent of our patients. The absence of such a communication may mean that drainage of the cyst alone is inadequate, at least in chronic pancreatitis. We do not use ERCP in the work-up of pseudocysts complicating acute pancreatitis for fear of infection, though Nealon and colleagues[25] have used it safely to refine their operative plan. On-table cystography, with or without separate ductography, allows a rational choice of drainage procedure (nearly always cystjejunostomy Roux-en-Y) or sometimes resection to incorporate an intrapancreatic cyst.

Pancreas divisum occurs in about 5 per cent of the population, but its clinical relevance is still disputed[26–28]. Unless the accessory duct can be cannulated endoscopically, pancreatitis cannot be excluded in the isolated dorsal pancreas. For patients with obscure abdominal pain, we have performed conservative caudal pancreatectomy (thus obtaining a histological specimen) followed by a prograde pancreatogram[29]. For those few with recurrent acute pancreatitis we prefer a transduodenal approach, cannulating each papilla and proceeding to sphincteroplasty after retrograde OTP[30].

Although operative pancreatography is described in the surgical literature[31,32], little attention has been drawn to the

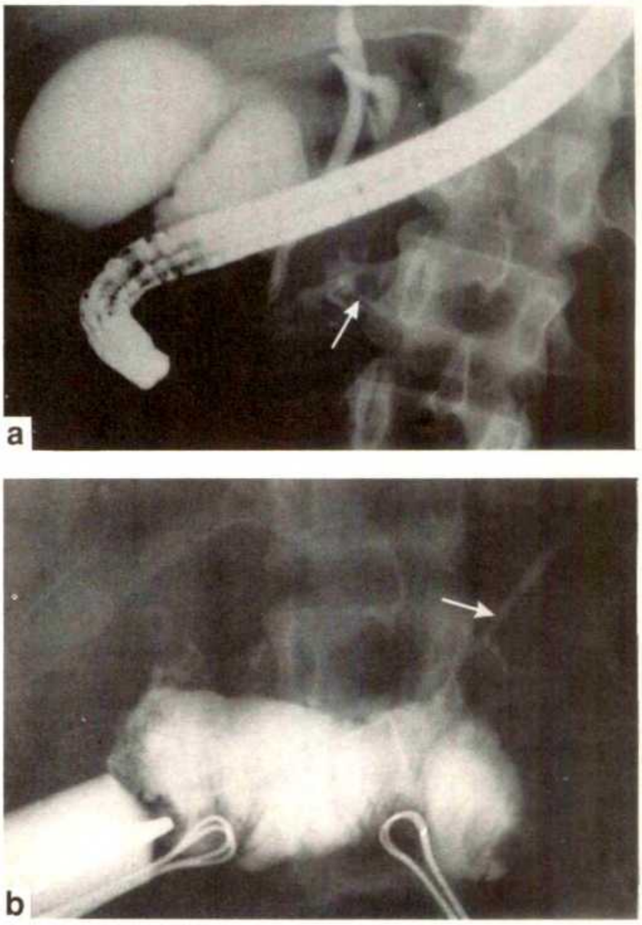

Figure 5 *Recurrent acute pancreatitis following longitudinal pancreaticojejunostomy (case 3).* **a** *ERCP shows an obstructing stricture in the head of pancreas (arrowed) and no filling of the bowel. An ascending loopogram performed at operation* **b** *shows anastomotic patency with free communication between the jejunum and unobstructed distal duct (arrowed)*

discrepancy in findings between ERCP and OTP. In our experience, OTP proved invaluable on 66 occasions when full visualization of the MPD was not achieved, giving important information on ductal morphology and resulting in a change of plan in 35 patients. We see a clear-cut role for this procedure in the full operative evaluation of pancreatic disease, particularly chronic pancreatitis and pancreas divisum.

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Laser recanalization *versus* endoscopic intubation in the palliation of malignant dysphagia

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Forty patients with widely disseminated or locally advanced malignant obstruction of the middle or lower third of the oesophagus underwent endoscopic treatment by either NdYAG laser recanalization or intubation. Groups were matched on the basis of tumour location and swallowing was graded clinically before and after treatment. Technical success was achieved in 17 of 20 laser treated and 18 of 20 intubated patients. Pretreatment swallowing ability, histology, tumour location and overall length were unrelated to functional outcome in both groups. However, circumferential tumour length identified endoscopically strongly influenced the quality of swallowing after laser recanalization. Patients with excellent swallowing quality ($n = 7$) *had significantly shorter circumferential tumour lengths, 3·1(1·0) cm, than those with poorer quality swallowing* ($n = 10$), *6·3(1·6) cm,* ($P < 0·001$). *Both methods of treatment had low complication rates and there was one death in the series in the laser-treated group. Laser recanalization provides a better functional result than intubation for short* (< 4 *cm) circumferential tumour. Intubation at a single session seems more appropriate than repeated laser therapy when tumour length exceeds 4 cm.*

Keywords: Oesophageal carcinoma, endoscopy, intubation, laser therapy

Dysphagia due to malignant disease is a common surgical problem and is usually caused by carcinomas of the oesophagus, cardia or bronchus. Ten years ago, Earlam and Cunha-Melo estimated that only about 40 per cent of patients with oesophageal cancer had resectable tumours[1] While the resectability rate may be considerably higher in specialist units[2], few surgeons would feel that surgery has much to offer patients who present with widespread metastases and there is undoubtedly a group of elderly individuals with severe concomitant medical problems who are unlikely to tolerate a major surgical procedure. Again, over the past 10 years, both endoscopic intubation and endoscopic laser therapy have established themselves as palliative therapies for those patients in whom surgery seems inappropriate[3–6]. Both techniques have their advocates, but a critical comparison has never been carried out. The purpose of this study was to perform a prospective comparison of endoscopic laser therapy and endoscopic intubation with particular reference to quality of survival.

Patients and methods

Patient details are outlined in *Table 1*. Forty patients were allocated to treatment by endoscopic intubation or endoscopic laser therapy Patients considered eligible for the study were those with primary tumours arising in the middle and lower thirds of the oesophagus or in the cardia, and those with anastomotic recurrences following previous surgery. Patients with tumours arising in the upper third of the oesophagus were excluded as it was felt that endoscopic laser therapy was superior to endoscopic intubation in this location Those patients with extrinsic invasion of the oesophagus or proven fistulae into the respiratory tract were also excluded Randomization was based on tumour location (*Table 2*) Nearly half the patients had visceral metastases which were diagnosed histologically in 12 patients and by computed tomographic (CT) scanning or chest radiography in seven Nine patients were considered unfit for surgery, four because of severe concomitant medical problems and five because of age and generalized debility Twelve patiens were considered to have unresectable tumours, seven of these 12 had anastomotic recurrences (four in the chest following oesophagogastrectomy and three in the abdomen following total gastrectomy), one had an unresectable tumour found at surgery, and four patients had not responded to radiotherapy (all had extensive local disease on CT scan).

All endoscopic procedures were carried out using intravenous midazolam (Roche Products Ltd., Welwyn Garden City, UK), employing either the Olympus XQ-20 or GIF IT-10 endoscopes

Table 1 *Patient details at time of treatment*

	Treatment group	
	Endoscopic laser therapy	Endoscopic intubation
No of patients	20	20
Mean age in years (range)	72 (49–89)	76 (55–91)
Sex (male:female)	13:7	15:5
Histology		
Adenocarcinoma	11	14
Squamous carcinoma	9	6
Indication for treatment		
Metastases	10	9
Unfit for surgery	3	6
'Unresectable'	7	5

Table 2 *Endoscopic details of tumour location and length*

	Treatment group	
	Endoscopic laser therapy	Endoscopic intubation
Tumour location		
Middle third	8	7
Lower third	9	9
Anastomotic recurrence	3	4
Mean(s.d.) overall tumour length, cm	6·4(2·07)	5·7(2·28)
Mean(s.d.) circumferential tumour length, cm	4·9(2·07)	4·1(1·38)

(Olympus KeyMed, Southend-on-Sea, UK). The endoscopic tumour location was documented and the overall and circumferential lengths of tumour recorded by marking the endoscope at the incisor teeth as it was withdrawn back through the tumour area. For technical reasons, therefore, some patients had their tumour lengths measured after recanalization (*Table 2*). Endoscopic laser therapy was performed using an NdYAG laser (Medilase, MBB-Medizintechnick, Swindon, UK). A non-contact technique was used at a setting of 90–100 W with two 1-s pulses at each point Dilatation was never used before the first laser treatment, but was used on an intermittent basis in association with subsequent treatments Technical success was considered to have been achieved when the 11·5 mm diameter endoscope could be passed easily beyond the treated area. After successful recanalization, repeated treatments were offered at intervals of 4 weeks.

Endoscopic intubation was performed after preliminary dilatation using either Celestin or Savary–Gilliard dilators over a guidewire Both Celestin (Medoc, Gloucester, UK) and Atkinson (KeyMed, Southend-on-Sea, UK) type tubes were used. Swallowing ability was graded clinically before and after treatment. 0, completely normal, I, aware of occasional solid food hold-up but no dietary modifications; II, consistent hold-up of certain solids with subsequent dietary modifications, III, unable to tolerate any solids and taking liquid diet only, IV, liquid regurgitation.

Chest radiographs were performed routinely immediately after both forms of treatment and patients in the laser group were further assessed by barium swallow and/or pull-through manometry

Results are expressed as mean(s d). Statistical analysis was by non-parametric methods employing the Wilcoxon rank sum test

Results

Technical success was achieved in 17 of 20 endoscopic laser therapy patients and in 18 of 20 endoscopic intubation patients. Of the 17 endoscopic laser therapy patients treated successfully, recanalization was obtained at a single session in 13 patients and in two sessions 3 days apart in the remaining four patients. The average energy delivery was 13 186 J per patient. Repeat sessions were performed at intervals of approximately 4 weeks, the total number of treatments received on average was four per patient, and the median survival for the group was 12 weeks (range 2–36 weeks). Of the three technical failures, one patient had a clinically unsuspected fistula which was identified distal to the laser-treated area when recanalization was achieved, one was withdrawn from the study after a single session of laser treatment as it was felt his life-expectancy was short, and a third patient developed a radiological oesophagotracheal fistula after a single laser session; this was subsequently treated satisfactorily by intubation. Of the patients treated successfully, one had a radiological perforation with air in the mediastinum and one had an intraperitoneal perforation, recognized endoscopically, from a tumour arising at the gastro-oesophageal junction. Both of these patients survived without additional complications on conservative therapy. There was one death from myocardial infarction, but this was probably precipitated by recurrent bleeding from the treated tumour surface 10 days after successful recanalization despite two subsequent attempts to photocoagulate the bleeding area.

All successfully treated patients experienced an improvement in the grading of their dysphagia The quality of swallowing, however, permitted only seven patients to enjoy a relatively normal diet (grades 0 and I), while the other ten patients all required some dietary modification (grades II and III). Only two patients, however, existed on a liquid diet alone, the overall lengths of their tumours were 8 and 12 cm respectively. While the overall tumour length identified endoscopically was similar in patients graded 0 or I after treatment, (mean tumour length 5·5(1·9) cm) and in those graded II and III after treatment (mean tumour length 6·9(2·1) cm) mean circumferential tumour length was significantly shorter in patients with better swallowing grades (0 and I, 3·1(1·0) cm), than those with poorer swallowing grades (II and III, 6·3(1·6) cm ($P<0·001$)).

Endoscopic intubation was performed successfully in 18 of 20 patients. There were two treatment failures In one patient angulation at an oesophagojejunal anastomosis caused by recurrence prevented the passage of a guidewire into the jejunal loop. In the other patient the intra-abdominal portion of the oesophagus was split during the preliminary dilatation immediately above a tumour at the gastro-oesophageal junction; this was dealt with by the insertion of a traction tube via laparotomy. There were no procedure related deaths in the intubation group, but there were three instances of distal tube migration in two patients and a single case of tumour overgrowth at the upper end of a prosthesis The median survival was 16 weeks. None of the patients had completely normal swallowing after intubation. Only two had grade I swallowing, 15 had grade II, and one patient existed solely on a liquid diet, although this was mainly because of anorexia.

The relative outcomes in the two groups are summarized in *Table 3*. Perforation, in this series, was more common after endoscopic laser therapy than endoscopic intubation. The need for retreatment following endoscopic laser therapy was present in nearly all cases (being a function of survival), although endoscopic intubation also had this problem occasionally owing to tube displacement or occlusion. Bolus obstruction of a tube did not occur.

Although five of the seven patients with local recurrence had tumours with an overall length of ≤4 cm, there was no statistically significant difference in mean overall length between this group and those patients with primary tumours (4·4(1·9) cm and 5·8(2·3) cm respectively).

Discussion

Both endoscopic laser therapy and endoscopic intubation provide effective palliation for nearly all patients with malignant obstruction of the oesophagus; 88 per cent of patients entered in this study had an improvement in their swallowing. Of the treatment failures who were subsequently excluded from this study one of the endoscopic intubation patients was successfully treated by laser and two of the laser failures were successfully intubated so that 95 per cent of such patients can be technically palliated

Technical success, however, did not correlate with functional outcome. Endoscopic intubation produced acceptable palliation but only two of the patients enjoyed a normal diet. While seven of 17 (41 per cent) laser patients experienced a much better quality of palliation in terms of swallowing ability, the majority (59 per cent) faired no better than the endoscopic intubation group.

These technical and functional results are similar to those reported in other large series, both after intubation[3,4,7–10] and laser recanalization[5,6,10–12]. Both techniques have low complication rates[3–12] Circumferential tumour lengths of <4 cm are best palliated by endoscopic laser therapy. A group of patients in which this regularly seems to be the case are those with anastomotic tumour recurrences, a finding previously noted by Fleischer and Sivak[13]. Of the seven patients with local recurrences in this series, five had circumferential tumour lengths of <4 cm (two endoscopic laser therapy, three endoscopic intubation). These small numbers preclude any statistical analysis but, bearing in mind the difficulties which can occur in intubating these recurrent strictures which result from angulation, endoscopic laser therapy probably represents

Table 3 *Outcome of treatment*

	Treatment group	
	Endoscopic laser therapy (%)	Endoscopic intubation (%)
Technical success	17 (85)	18 (90)
Perforation	3 (15)	1 (5)
Haemorrhage	1 (5)	0 (0)
Retreatment	16/17 (94)	2/18 (11)
Deaths	1 (5)	0 (0)

the most appropriate first treatment. Conversely, patients with circumferential tumours >4 cm are unlikely to achieve better quality palliation from endoscopic laser therapy than from endoscopic intubation. Because endoscopic laser therapy results in a greater need for readmission to maintain patency, endoscopic intubation should be the preferred primary treatment for this group.

Laser recanalization and intubation should be regarded as complementary rather than mutually exclusive techniques. Each has a role in both the production and maintenance of oesophageal patency and both can be used in conjunction with other modes of therapy such as intracavitary irradiation. It is unfortunate that endoluminal irradiation has so far not added significantly to the quality of survival[14,15], and surgeons should remember that the best quality palliation is achieved by oesophageal resection[2]. Nevertheless, identification of a group of patients with a very short life-expectancy in whom surgery does not seem justifiable is usually not difficult and for such a group, similar to that described in this study, intubation or laser therapy can be chosen appropriately to provide effective relief from dysphagia.

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Stress in surgeons

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A sample of 1000 members of the Association of Surgeons of Great Britain and Ireland was circulated with a postal questionnaire relating to their occupational stressors, their type A coronary-prone behaviour and their mental health. Six hundred and seventy-two (67 per cent) useable forms were returned anonymously. The major individual stressors were: (1) the interference of the job with personal life, (2) general administration, and (3) the number of patients in clinics. Type A behaviour was similar to that of other professional groups. Surgeons showed mean scores significantly higher than the general population on two subscales of the mental health index (free-floating anxiety and hysterical anxiety). The findings for the few female surgeons (2 per cent) were similar to those in men but they did not exhibit raised free-floating anxiety levels.

Keywords: Surgeons, stress, type A behaviour pattern, Crown–Crisp Experiential Index

Psychological stress is a particular relationship between the person and the environment that is appraised by the person as taxing or exceeding his/her resources and endangering his/her well-being. Since the 1960s there has been a growing recognition that, while stress is an inevitable aspect of the human condition, it is coping that makes the main difference in adaptational outcome. In recent years this understanding of stress has been used to identify the contribution it plays in illness. It has been suggested that there are two central features of stress at work[1], the interaction of which leads to either coping or to maladaptive behaviour and stress-related disease. These features are the characteristics of the person and the potential sources of stress in the work environment. Together they form the person–environment fit. In addition to this there is a further set of extra-organizational variables which can be stress-inducing. These relate to outside relationships or events.

According to the Annual Report issued by the Department of Health and Social Security in 1968[2], men lost 22 8 million working days due to various forms of mental ill health This was second only to bronchitis in the league table of illness and lost working days. It has been estimated that cardiovascular diseases accounted for 12 per cent of the time lost by the working population in the USA[3]. This, together with coronary heart disease and mental ill health, represents a serious cost for industry in both financial and human terms. In the 1970s occupational stress was suggested as a causal factor in these diseases[4]. Negative environmental factors such as work overload and role conflict were seen as occupational stressors. However, in addition to the environmental precursors, inherent characteristics of individuals and their behaviour may also contribute to occupational ill health.

Measurements of heart rate as an indication of stress in surgeons has been advocated[5] Another study[6] demonstrated that oral and maxillofacial surgeons had increased heart rate and rhythm while local and general anaesthetics were administered. It was suggested that administration of general anaesthetic was the more stressful. In the early 1960s workers began investigating individual stress differences and behaviour patterns after a relationship between a certain type of behaviour pattern and the prevalence of coronary heart disease had been noticed[7] Later two main types of behaviour patterns, type A and type B, were identified[8]. Type A behaviour is characterized by achievement, competitiveness, time urgency, devotion to work and a preoccupation with deadlines, whereas type B behaviour is characterized by the relative absence of the behaviour associated with type A. Moreover, there are strong indications that there are some work environments which not only enhance but actually reward type A behavioural traits

There has been increasing concern over the disabled physician in the USA[9] and the sick doctor in Britain[10] and stress is recognized as affecting a substantial proportion of doctors at various stages throughout their careers. A number of studies have shown higher than average rates of mental illness, alcoholism, drug abuse and marital problems among the medical profession[11–13]. Problems such as malpractice suits, threats of physical harm, the changing practice towards defensive medicine and the pressure of peer review were found to be some of the most common causes of stress in medical practice in the USA[14]. There may well be similar patterns of problems in this country, and certainly a major stressor of the pre-registration year is over-work[15]. In a study of the health of 466 doctors in Switzerland[16], 77·7 per cent had suffered from at least one disease during the year studied; in 50 per cent of cases the morbidity was linked to stress and emotivity. Cardiovascular pathology was significantly higher than in the average population. General practitioners, psychiatrists and surgeons appeared to be especially exposed to stress and emotivity.

The present study investigates the relationship between some of the possible causes of stress in surgeons, including demographic, personality and work factors, and certain manifestations of mental ill health.

Methods

A questionnaire was formulated which included three major types of independent variable measures (biographical factors, a personality measure obtained from the type A/B behaviour questionnaire and an occupational stressor inventory) and one dependent variable, the mental health index.

The sample

The questionnaires were distributed by the Association of Surgeons of Great Britain and Ireland to a systematic sample of 1000 of its members selected by using 10 out of every 11 names on the Association's mailing list

Independent variables

The independent variables were demographic/biographical details, the type A/B behavioural questionnaire and the occupational stressor inventory.

Demographics This covered biographical material such as age, sex, marital status, number of children, present grade, years in post, type of hospital, number of sessions worked (National Health Service (NHS) and private), details concerning 'on call' and number of leisure hours per week.

Type A/B behaviour questionnaire. This was formulated by Bortner and Rosenman[17] and was used to assess the extent to which subjects

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possessed stress-prone personalities. The questionnaire consisted of 14 bipolar adjectival scales which were measured on a continuum and 11 points were assigned to each scale. High scores indicated type A behaviour and low scores type B behaviour. The available range was 14–154.

Work stressor inventory. This was formulated from discussions with a number of surgeons, plus additional items generated from pertinent findings reported in the literature on stress in other professional workers. The inventory consisted of 24 statements describing potentially stressful work-related conditions. The subjects were required to rate each item along a six-point Likert-type scale ranging from 'no stress' (1) to 'high stress' (6).

Dependent variable

Mental health index. The Crown–Crisp Experiental Index[18], formerly the Middlesex Hospital Questionnaire, was used to measure the psychological well-being and mental health of the subjects. It aims to reveal various types of anxieties, obsessions and depressions. This questionnaire is composed of 48 items which are categorized into six subscales of mental health. free-floating anxiety, phobic anxiety, obsessionality, somatic anxiety, depression and hysterical anxiety. The reliability and validity of the mental health index have been established[18]

Data analysis

The data were analysed using the statistical package SPSS-X (SPSS Inc., Chicago, Illinois, USA) on the mainframe computer at the South Western Universities Regional Computer Centre. Univariate and multivariate statistical analyses were carried out including frequency distributions, *t* tests, χ^2 analyses, correlations and a principal component analysis[19].

Results

A total of 690 questionnaires was returned (a response rate of 69 per cent). However 18 forms had to be discarded: six because they were not fully completed, four since the questionnaire was no longer applicable (e.g. they were no longer working in this country), and the rest were returned after the analysis was completed.

The sample of 672 consisted of 657 (98 per cent) men and 15 (2 per cent) women, ranging in age from early 30s to 70 years old, 81 per cent being aged between 40 and 60 years; 95 per cent were married with an average of 2·5 children; 14 per cent had been married previously. Thirty-five (5 per cent) of the sample were senior registrars and 636 (95 per cent) were consultants Five hundred and seventy-eight (87 per cent) worked principally for the NHS whereas 84 (13 per cent) were honorary consultants.

Over half the sample had been in their post for 10 years or less. Three hundred and thirty-seven respondents (50 per cent) regarded themselves as general surgeons only, 229 (34 per cent) were general surgeons but acknowledged some degree of specialization and 105 (16 per cent) felt that they were specialist surgeons only Two hundred and forty-one (36 per cent) worked at a teaching hosital, 304 (45 per cent) worked at a district general hospital but also did some teaching while 97 (15 per cent) worked at a district general hospital without teaching and 27 (4 per cent) worked elsewhere, either in the Armed Forces or in Ireland. Twenty-four per cent were full-time NHS and a further 45 per cent worked ten NHS sessions, whereas only 1 per cent worked six or more private sessions and 52 per cent worked one or less private sessions per week. On-call rotas varied from one in two to none, with 50 per cent working one in four or more frequently. There was a very wide range for the number of hours worked while on-call (0–98 h) with 50 per cent working 4 h or less. Forty-five surgeons did not complete the questionnaire on leisure hours: a much higher default rate than for any other question. The number of leisure hours varied widely from 0 (ten surgeons) to 40 or more (eight surgeons) with 75 per cent claiming 10 h or less per week.

Type A behaviour pattern

The mean score for the test, in a range of 41 to 136, was 89·6 and this is not dissimilar to other professional normative populations.

Work stressor inventory

Each of the work stressors scored between 1 (no stress) and 6 (high stress) (*Table 1*). Although each one caused some surgeons little stress, all caused other surgeons high stress. The greatest individual stressor was 'job interferes with personal life': over 50 per cent of the subjects scored 4 or more on this item and it had a median of 5, whereas 'number of patients in clinics' and both 'nursing administration' and 'general administration' had a median of 4.

When the 34 work stressors were analysed, seven factors with an eigenvalue greater than 1 were extracted by principal component analysis. Together these accounted for 56 per cent of the total variance. A varimax rotation was carried out (*Table 2*). The resultant factors have been labelled external theatre pressures, internal theatre pressures, patient pressures, nursing and administration pressures, back-up support services pressures, technical support services pressures, job encroaching on life pressures. For each factor *Table 2* lists the variables with a coefficient of 0·25 or more together with the coefficients themselves.

Mental health

The normative populations for the Crown–Crisp Experiential Index, with which the surgeons have been compared, were described fully by Crown and Crisp[18]. In general, women tended to score more highly than men, as indeed they do in the present study, suggesting a lower mental well-being.

The comparisons with their respective normative populations for each subscale are shown in *Figures 1–6* Male surgeons had significantly higher scores on two subscales: (1) free-floating anxiety (*Figure 1*) ($t = 7·43$, d.f. = 656, $P < 0·001$ with a 95 per cent confidence interval of 3·4–3·8 for the population mean, compared with the normative value of 2·8); (2) hysterical anxiety (*Figure 6*) ($t = 19·20$, d.f. = 656, $P < 0·0001$ with a 95 per cent confidence interval for the population mean of 4·9–5·4 *versus* 2·9). Women, on the other hand, only showed higher hysterical anxiety ($t = 3·93$, d.f. = 14, $P < 0·01$; 95 per cent confidence interval for the population mean of 4·4–7·9 *versus* the normative value of 2·9).

Comparisons between groups of surgeons. Senior registrars were significantly more stressed by training pathways ($t = 7·98$,

Table 1 *The means and standard deviations of the work stressor inventory*

	Mean	Standard deviation
Job interferes with personal life	4·23	1·36
Outpatient facilities	2·85	1·41
Need to teach	2·45	1·23
Changes to lists	1·99	1·33
Lack of theatre availability	3·03	1·71
Theatre support staff	2·79	1·51
Availability of beds	3·43	1·69
Secretarial support	3·00	1·72
Junior medical support	2·58	1·40
Filling in for juniors	2·65	1·48
Nursing standards	2·90	1·38
Nursing administration	3·50	1·54
General administration	3·88	1·47
Intensive care facilities	2·55	1·71
All day operating	2·22	1·44
Waiting lists	2·86	1·60
Patient non-attendance	2·05	1·19
No. of patients in clinics	3·66	1·56
Practical operating	1·92	1·17
Complex surgery	2·79	1·49
Professional isolation	2·08	1·40
Training pathways	3·03	1·83
Pathology services	1·95	1·17
Radiology services	2·26	1·36

Table 2 *Varimax rotated principal components of work stressors for surgeons*

Factor 1: External theatre pressures	
Theatre availability	0·851
Time changes to theatre lists	0·711
Theatre support staff	0·671
Availability of beds	0·483
Intensive care facilities	0·377
Secretarial help	0·371
Factor 2. Internal theatre pressures	
Practical operating	0·856
Complex surgery	0·853
All day operating	0·635
Need to teach	0·300
Professional isolation	0·281
Factor 3. Patient pressures	
Number of patients in outpatient clinic	0·770
Outpatient facilities	0·653
Length of waiting lists	0·632
Patients' non-attendance	0·430
Need to teach	0·289
Availability of beds	0·271
Factor 4. Nursing and administration pressures	
Nursing administration	0·873
General administration	0·745
Nursing standards	0·606
Availability of beds	0·278
Factor 5: Backup support services pressures	
Junior medical support	0·813
Need to cover juniors when on leave	0·809
Professional isolation	0·440
Secretarial support	0·278
Factor 6: Technical support services pressures	
Pathology services	0·744
Radiology services	0·736
Intensive care facilities	0·501
Outpatient facilities	0·258
Factor 7: Job encroaching on life pressures	
Job interferes with personal life	0·695
Training pathways	0·651
Professional isolation	0·366
Availability of beds	0·345
Length of waiting lists	0·296

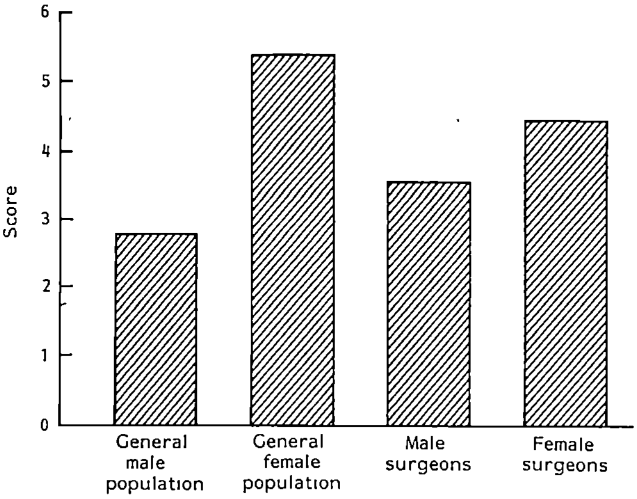

Figure 1 *Crown–Crisp scale Free-floating anxiety levels in male and female surgeons in comparison with those of the general population*

d.f. = 40·84, $P < 0·0001$), the job interfering with their personal life ($t = 2·91$, d.f. = 39·00, $P < 0·01$), availability of beds ($t = 2·43$, d.f. = 39·63, $P < 0·02$) and lack of theatre ($t = 2·56$, d.f. = 38·28, $P < 0·02$) than were consultants. Consultants, however, were more stressed by general administration than were senior registrars ($t = 2·51$, d.f. = 665, $P < 0·02$).

Honorary consultants were signicantly more stressed than were NHS consultants by lack of theatres ($t = 3·50$, d.f. = 660, $P < 0·001$), secretarial support ($t = 2·74$, d.f. = 660, $P < 0·01$) and intensive care facilities ($t = 2·74$, d.f. = 660, $P < 0·01$) However, NHS consultants were significantly more likely to be stressed

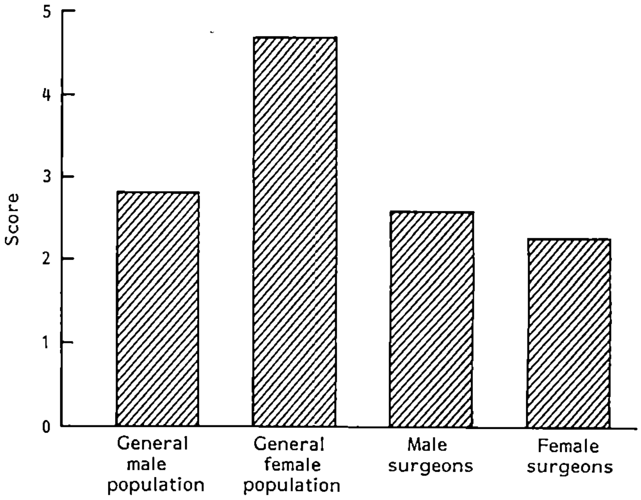

Figure 2 *Crown–Crisp scale. Phobic anxiety levels in male and female surgeons in comparison with those of the general population*

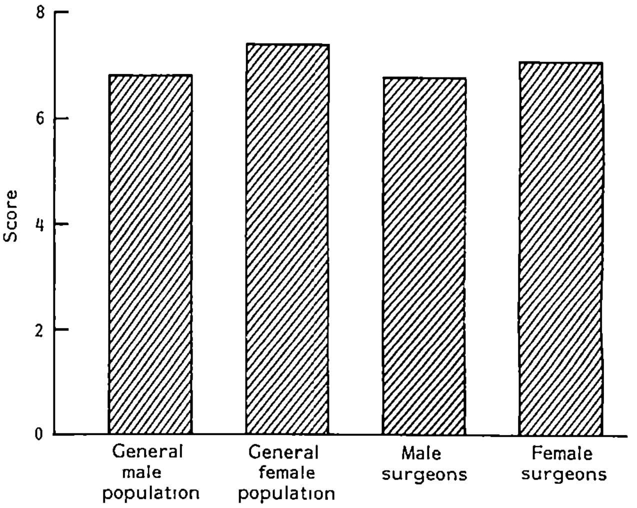

Figure 3 *Crown–Crisp scale. Obsessionality in male and female surgeons in comparison with those of the general population*

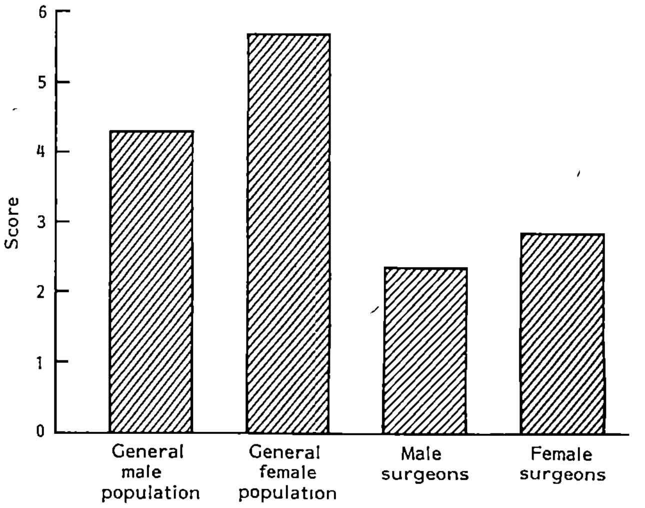

Figure 4 *Crown–Crisp scale Somatic anxiety in male and female surgeons in comparison with those of the general population*

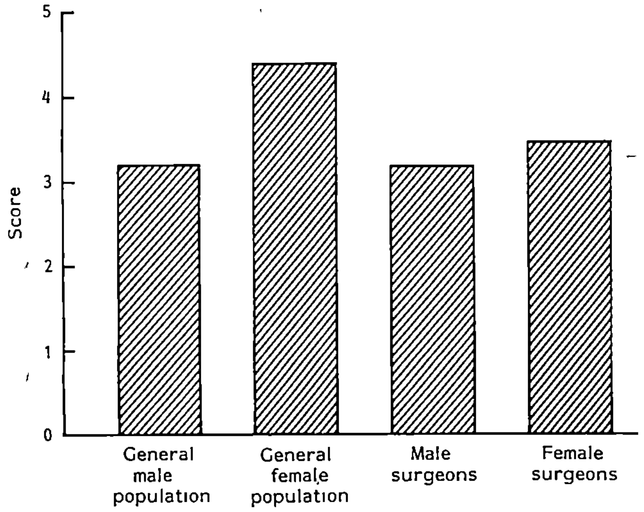

Figure 5 *Crown–Crisp scale Depression in male and female surgeons in comparison with those of the general population*

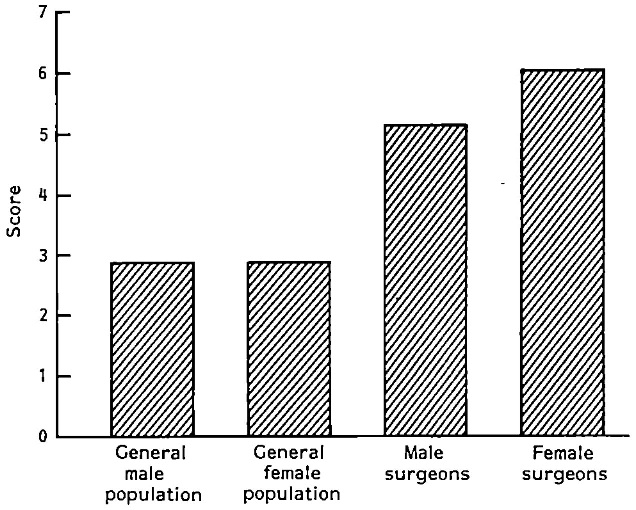

Figure 6 *Crown–Crisp scale. Hysteria scores in male and female surgeons in comparison with those of the general population*

by the number of patients in clinics than were honorary consultants ($t=2{\cdot}80$, d.f. $=108{\cdot}2$, $P<0{\cdot}01$). Honorary consultants had significantly higher scores (type A) on the Bortner scale ($t=4{\cdot}10$, d.f. $=132{\cdot}00$, $P<0{\cdot}0001$).

When the surgeons were divided into two groups by age (overall mean(s.d.) 48·5(7·7) years), younger surgeons were significantly more stressed by 'job interfering with personal life' ($t=4{\cdot}47$, d.f. $=615{\cdot}05$, $P<0{\cdot}0001$), 'training pathways' ($t=4{\cdot}85$, d.f. $=638$, $P<0{\cdot}0001$) and 'lack of theatre time' ($t=2{\cdot}05$, d.f. $=670$, $P<0{\cdot}004$) than were older surgeons. However, the older surgeons were more stressed by 'general administration' ($t=2{\cdot}42$, d.f. $=666$, $P<0{\cdot}02$). Younger surgeons also scored significantly more highly (type A) on the Bortner scale ($t=2{\cdot}14$, d.f $=667$, $P<0{\cdot}03$) and the hysterical anxiety scale ($t=3{\cdot}39$, d.f. $=665$, $P<0{\cdot}001$) than older surgeons. The younger surgeons were significantly less depressed ($t=3{\cdot}19$, d.f. $=670$, $P<0{\cdot}001$) and suffered from less somatic anxiety ($t=3{\cdot}83$, d.f. $=670$, $P<0{\cdot}0001$) than older surgeons.

Discussion

A return rate of 69 per cent to the questionnaire was not unreasonable considering that the emphasis on total anonymity precluded any personal follow-up of non-respondents. The findings relate mainly to male surgeons who accounted for 98 per cent of this sample. Extrapolation of the findings regarding the women should be exercised with great caution due to their very small representation.

Both the Bortner type A behaviour scale and the Crown–Crisp Experiential Index have been used with other professional groups and thus it was interesting to compare the surgeons with some of the other groups studied. Although there are equal numbers of type A and type B personalities in the population as a whole[20], few white collar occupational groups appear to have a mean below 90. In a survey of general dental practitioners[21] the mean score was just above 90, whereas head teachers and principals in another study[22] had higher mean scores of 102, indicating higher risk status. These compared with the surgeons' mean score of 89·6. The surgeon population worked long hours, was frequently on call and did not have much leisure time. For all these groups the very nature of the work environment rewards type A behaviour pattern personalities. There has been much research into the type A behaviour pattern over the last two decades and some revaluation[23]. Nevertheless, it was advantageous to be able to demonstrate that the surgeons showed similar scores to the other professional groups. The head teachers and principals were particularly stressed by their management role, and it is interesting to speculate that if we had been able to identify the surgeons taking a large part in management, then their type A scores might have been raised.

Other stressed professional groups showed raised scores on some of the subscales of the Crown–Crisp Experiential Index. Male general dental practitioners[21] had raised scores on four subscales (free-floating anxiety, phobic anxiety, depression and hysterical anxiety) compared with the normative population. In addition the head teachers' survey[22] revealed significantly higher scores on three subscales (free-floating anxiety, depression and hysterical anxiety). The surgeon population was different from these other groups in having only two raised scores, free-floating anxiety and hysterical anxiety. Free-floating anxiety is concerned with non-specific generalized anxiety. Amongst the surgeons it was clearly associated with most of the items on the work stressor inventory and most strongly with 'job interferes with personal life'. The hysterical anxiety scale is concerned with individuals who crave love and attention and who like to over-dramatize situations. It has also been suggested[24] that the hysteria subscale is associated with extraversion and sociability. These findings might be thought to lend support to the layman's stereotype of the 'Sir Lancelot' surgeon.

There were also differences between the different groups of surgeons. Senior registrars needed to be available for and actually worked longer hours than consultants. Hardly surprisingly they were more concerned by how this interfered with their personal life. Indeed, their concern over availability of beds and theatres could also be partly due to the time involved in dealing with these factors.

The honorary consultants were the group demonstrating the highest scores (for this population) on the Bortner scale but they were less depressed that the NHS consultants. Possibly academic life is more pressured and this encourages and rewards type A personalities! Perhaps the price one pays for a more pressured work pattern is the raised potential for coronary heart disease but the bonus is that one is less depressed.

As surgeons become older and more senior they become more stressed by 'general administration'. This has implications for the surgeons in the present round of NHS reforms. Indeed, the personal cost to the surgeons could well be more stress.

Finally, in any attitude-type survey it has to be remembered that the data indicate the way in which the respondents see themselves. Correspondence received whilst this survey was in progress has suggested that their wives and families believed that some surgeons were underestimating their stress levels. So it is possible that their perceived stress levels are an underestimation.

In conclusion, surgeons showed significantly higher mean scores than the general population for free-floating anxiety and hysterical anxiety. Scores for type A coronary-prone behaviour were similar to those of other professional groups.

The major individual stressors were interference with personal life, general administration and the number of patients in clinics. When stressors were grouped by principal component analysis some of the major effects were due to the groupings described earlier as 'external theatre pressures', 'internal theatre pressures' and 'patient pressures'.

Senior registrars were on call more frequently than consultants and actually worked in hospital more than double the hours when on call. They were significantly more stressed than consultants by training pathways, their job interfering with their private life and the availability of beds.

Honorary consultants were more likely than NHS consultants to show type A behaviour pattern but less likely to be depressed. They were also significantly more stressed than NHS consultants by theatre availability, secretarial help and intensive care facilities.

Younger surgeons were more likely to exhibit a type A behaviour pattern and have higher free-floating and hysterical anxiety than were older surgeons but were less likely to suffer from somatic anxiety or depression. As surgeons become older and more senior they become increasingly stressed by general administration.

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Aetiology of pancreatic cancer

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Curative surgery is possible in only a small minority of patients with pancreatic cancer and, to date, responses to chemotherapy and radiotherapy have been disappointing. To make any impact on the incidence of the disease a clearer understanding of its aetiology is required. This review explores present knowledge of the aetiology and epidemiology of pancreatic cancer.

Keywords: Pancreatic cancer, aetiology, epidemiology

The incidence of pancreatic cancer has increased steadily in the past 60 years throughout the world. Epidemiological studies have attempted to shed some light on the aetiology of the disease, but our understanding of factors that initiate and promote the development of pancreatic cancer remains poor.

Pancreatic cancer is now the fourth leading cause of cancer death in the USA after lung, colorectal and breast cancer[1] Between 1920 and 1970 the age-adjusted mortality rate for pancreatic cancer in the USA increased from 2·9 per 100 000 to nine per 100 000[2], while in England and Wales its incidence doubled between 1930 and 1970[3]. In 1950, the mortality rate for pancreatic cancer in Japan was one per 100 000 population but by 1974 this had risen to nearly six per 100 000 population[4]. In recent years it has been suggested that the annual incidence in the USA is now levelling off at approximately ten new cases per 100 000 population[5].

The incidence of pancreatic cancer varies with age, sex and race. In most countries the incidence is higher in men than in women by a ratio of about two to one[4]. The disease is rare in those under 25 years of age and is uncommon under the age of 45 years[6]. Over 80 per cent of cases occur in the 60–80 years age group[5]. Although pancreatic cancer is more common in Western or industrialized countries, the highest incidence reported in men occurs in New Zealand Maoris, native Hawaiians and black Americans, while in women, Hawaiians, Latins and Maoris have the highest reported incidence. The lowest rates reported to date are in Nigeria and India. In the USA, in both sexes, blacks appear to have a higher rate of pancreatic cancer than whites[7].

It is unclear whether reported geographical and racial demographic differences represent differences in genetic susceptibility to the development of pancreatic cancer, or differences in exposure to environmental and socioeconomic influences. Studies of migrating populations, which have been useful in investigating the aetiology of other forms of cancer, have shed little light on the aetiology of pancreatic cancer. In 1957, Smith reported on the incidence of pancreatic cancer among Japanese immigrants to the USA[8]. These immigrants had a higher incidence of pancreatic cancer than native Americans or Japanese living in Japan. The pancreatic cancer risk to American-born offspring of such Japanese migrants to the USA was at a level between those of the native populations of the two countries in subsequent studies[9,10]. It has been suggested that this discrepancy in incidence rates might be explained by undercertification of pancreatic cancer deaths in Japan or by incorrect certification of some deaths as due to gastric cancer, a more common tumour in that country[9,11]. Similarly confusing migrant studies have been carried out on the Negro populations of USA; in one study, northward migrating Negroes born in the south of the USA assumed a higher incidence rate than Negroes born in the northern state of Ohio[12].

Some religious groups appear to have a higher than average susceptibility to develop pancreatic cancer. In studies based in New York City, pancreatic cancer occurred more frequently among Jews than Catholics or Protestants[13,14]. Similar findings were reported by Siedman in 1970 and the differences were particularly striking when Jewish and non-Jewish women were compared[15]. Enstrom reported that Utah Mormons had a lower risk of developing pancreatic cancer than a National Center for Health Statistics group of non-smoking white American men[16] although a previous Utah-based survey demonstrated low rates of pancreatic cancer in both Mormons and non-Mormons[17].

Smoking

Many epidemiological studies have indicated that the most consistent risk factor for the development of pancreatic cancer is cigarette smoking. In 1966, following a study of US veterans, Kahn reported a relative risk in cigarette smokers compared with non-smokers of 1·84:1 (Reference 18). In the same year, Best demonstrated a dose–response relationship between the number of cigarettes smoked and the mortality rate from pancreatic cancer[19]. This finding has been confirmed by others[20–23]. However, caution must be exercised in the interpretation of some of these studies. Case–control studies in particular suffer from a number of pitfalls which are clearly elucidated in a paper by Feinstein *et al.*[24].

In 1976, after a 20-year prospective study, cigarette smoking male doctors were shown to have a relative risk of dying from pancreatic cancer compared with non-smokers of 1·6:1 (Reference 25). While this difference did not reach statistical significance, the authors concluded that there was a marginally significant trend, in that a higher rate of cigarette consumption did confer increased risk, and indicated that pancreatic cancer was positively associated with cigarette smoking. At about the same time, a Swedish group reported a mortality ratio of 3·1:1 for cigarette smoking men and of 2·5:1 for women[26].

It has been suggested that cigarette smoking doubles the risk of developing pancreatic cancer present in a non-smoking population[7] The increased risk of developing pancreatic cancer does not seem to apply to pipe or cigar smokers[18,27] although not all authors have agreed with this assertion[19,28]. Krain provided circumstantial evidence in support of the role of cigarette smoking by indicating that the incidence in cigarette smoking from 1940 to 1970 in the USA paralleled the increase in pancreatic cancer[29]. This conclusion was supported in a study of smoking trends and pancreatic cancer mortality rates in the USA between 1920 and 1978[30]. It demonstrated that the mortality rate for pancreatic cancer closely shadowed rises and falls in the incidence of cigarette smoking. This relationship was more striking in men than in women. Unfortunately, both of these papers can be criticized on methodological grounds in that the figures used to calculate mortality trends were not entirely comparable.

Despite a substantial body of published data supporting the relationship between smoking and pancreatic cancer, there have

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been a number of studies which have failed to demonstrate this relationship. In a study of cancer incidence and mortality in different countries published in 1975, Armstrong and Doll failed to demonstrate any relationship between smoking and pancreatic cancer[31]. Surprisingly, they also failed to demonstrate a strong relationship between lung cancer and cigarette smoking and admitted that there were considerable problems with the analytical methods used in their study. They also emphasized that failure to demonstrate a correlation between two variables in a population does not necessarily exclude a relationship in individuals. Binstock and colleagues reported a weak but statistically non-significant relationship between pancreatic cancer and smoking in a study concerned primarily with the putative link to coffee consumption[32]. In a retrospective case–control study, Durbec *et al.* reported an association between pancreatic cancer and alcohol consumption and smoking taken together, although alcohol seemed to be more important than tobacco[33]

While it seems likely that cigarette smoking does increase the risk of developing pancreatic cancer, the mechanism involved remains obscure. Wynder hypothesized in 1975 that tobacco smoke might influence the development of pancreatic cancer in three ways: (a) carcinogens in tobacco excreted in bile might reflux into the pancreatic duct, (b) tobacco carcinogens might reach the pancreas via the bloodstream; and (c) cigarette smoking can increase blood lipids which, in turn, might influence the development of pancreatic cancer[34]. While certain nitrosamines have been shown to be carcinogenic in experimental animals, none of the nitrosamines in cigarette smoke has yet been shown to cause pancreatic cancer in this setting The suggestion that reflux of carcinogen-containing bile into the pancreatic duct might be responsible for the development of pancreatic cancer is plausible, and pancreatic cancer in humans occurs most frequently in the head of the gland[35]. In addition, it has been demonstrated in humans that certain variations in the anatomy of the common bile duct and pancreatic duct at the sphincter of Oddi can allow bile to reflux from the bile duct into the pancreatic duct[36]. On the other hand, DiMagno and colleagues demonstrated an increase in pancreatic ductal epithelial abnormalities in patients who lacked a prominent common channel between the two ducts[37], although Armstrong and Taylor suggested that bile reflux into the pancreatic duct was more likely in patients with a long functional common channel[36]. It remains unclear whether this mechanism is relevant to the development of pancreatic cancer in humans.

Diet

Demographic differences in the incidence of pancreatic cancer throughout the world have prompted an extensive search for dietary factors which might be implicated in the disease. In particular, consumption of a 'Western diet' seems to increase the relative risk, and Doll and Peto have suggested that in the USA one-third of all cancer deaths could be attributed to dietary factors[38].

In 1967, Lea reported a significant correlation between the incidence of pancreatic cancer in various countries and per capita consumption of fats, oils, sugar, animal protein, eggs and milk[39] There was a significant positive correlation between pancreatic cancer and a high meat, low vegetable intake in men, and a low vegetable intake in women in a Japanese study published in the following year[40]. Unfortunately, dietary histories in this latter study were obtained from relatives by questionnaire in many instances Certainly, there is a significant correlation between pancreatic cancer death rates in different countries and the average per capita daily consumption of fat[41,42]

In a large follow-up study from Japan, Hirayama reported that daily, or more frequent, consumption of meat was associated with an increased risk (1·5:1), of developing pancreatic cancer[43]. This association, although weak, was statistically significant. It has been suggested that the great increase in the incidence of pancreatic cancer in Japan might be related to Westernization of the Japanese diet with documented increases in protein and fat consumption[28,44]. A high intake of fat was implicated in the aetiology of pancreatic cancer in two papers published in 1983[32,33]. In a case–control study, Gold and colleagues reported an association between pancreatic cancer and the consumption of white bread, while risk appeared to decrease with the consumption of raw fruits, vegetables and 'diet soda'[45]. In a large study based in Louisiana, pancreatic cancer was associated with consumption of pork products and rice, while fruit consumption seemed to offer some protection[46]. In a study of 34 000 Seventh Day Adventists from California (whose religion proscribes smoking, drinking alcohol or pork consumption), 50 per cent of whom eat a lacto-ovovegetarian diet, Mills and co-workers reported a lower than expected mortality rate from pancreatic cancer (although the reduction was not statistically significant)[47]. They also observed that the increased risk due to consumption of meat, eggs and coffee was lost when the data were controlled for cigarette smoking and that a high consumption of vegetables and fruits seemed to exert some protective effect.

It is interesting to note that in animals, dietary fat and protein increase the susceptibility to nitrosamine-induced pancreatic cancer[48–50] while retinoids inhibit carcinogenesis[51,52].

Exactly why dietary factors should influence the development of pancreatic cancer remains unclear. Dietary fat and protein are potent stimulants to the release of many gastrointestinal hormones. Many workers have shown that in animals, exogenous administration of hormones such as cholecystokinin and secretin can cause pancreatic hypertrophy and potentiate the development of pancreatic cancer[53–56]. Diets rich in raw soya flour, a trypsin inhibitor, can also promote the effect of the pancreatic carcinogen azaserine in rats[57] It has been suggested that diets rich in fats and protein stimulate the release of cholecystokinin and other hormones which act to increase pancreatic cell turnover, and thus increase the susceptibility of the gland to the effects of carcinogens[6]

Nitrosamines, which induce pancreatic cancer in hamsters, have been shown to be formed during cooking and in the stomach from nitrites and nitrates used in the preservation of meats[58,59]. The average daily intake of volatile nitrosamines in different countries has been shown to vary from 0·6 to 2 μg per person per day, although actual values depend on local food habits and preparation[60,61]

The role of vitamins in the development of cancer of various organs has received considerable attention in recent years. Vitamins C and E have been shown to inhibit or reverse nitrosation in experimental conditions[62] and this might explain the inverse correlation between pancreatic cancer risk and fruit and vegetable consumption noted earlier[45] Low serum levels of vitamin A (retinol) have been reported as being associated with an increased risk of cancer[63] although a subsequent report from the same group suggested that low serum retinol levels might be a consequence of cancer metabolism rather than a risk factor for cancer development[64].

Coffee consumption

The role of coffee in the aetiology of pancreatic cancer has been the subject of much controversy in recent years. In a comparison of age-adjusted death rates from various cancers and annual consumption of cigarettes, tea and coffee in a number of countries, Stocks reported a positive correlation between coffee consumption and pancreatic cancer in males but not in females[65]. In a large case–control study, MacMahon and colleagues found a highly significant association between coffee consumption and the risk of pancreatic cancer even when the data were adjusted to take cigarette smoking, age and sex into account[66]. There seemed to be a dose–response relationship in that risk increased in proportion to the number of cups of coffee consumed. MacMahon himself subsequently urged caution in the interpretation of this work, given that the control group was not thought to be ideal[67] and the detailed commentary on his paper used to highlight deficiencies in case–control studies in general has already been cited in this review[24]. In a more recent case–control study, MacMahon's group reported a slightly increased risk of pancreatic cancer only in those whose coffee consumption exceeded five cups per day[68]. They concluded that any association between pancreatic cancer and coffee consumption was not as strong as their initial data had suggested

The relationship between coffee consumption and pancreatic cancer was demonstrated in a cross-population study[32] but a consistent link was not confirmed in a subsequent case–control study in Los Angeles[22]. In addition, Mack *et al.*[22] found no link between pancreatic cancer and previous levels of consumption of tea, carbonated drinks, beer or spirits. Similar results were reported by Gold and associates from Baltimore, although there seemed to a dose–response relationship with coffee drinking in women, albeit not statistically significant[45] A more recent Italian study reported that coffee consumption was associated with a small increase in the risk of pancreatic cancer, but stressed that the interpretation of available data is complicated by other possible aetiological factors, such as cigarette smoking[69].

In 1981, Lin and Kessler reported a relationship between decaffeinated coffee consumption and pancreatic cancer[70] although more recent studies have failed to confirm this relationship[68,69,71,72] Wynder and his group showed no relationship between decaffeinated coffee consumption and pancreatic cancer in males, in females an association existed when one or two cups per day were consumed but was lost at higher levels of consumption[72].

Chronic pancreatitis

A familial form of chronic pancreatitis was first reported in 1952[73]. The disease seems to be inherited as an autosomal dominant trait with incomplete penetrance, and other affected families have since been reported[74–76]. Approximately one-third of affected patients develop pancreatic cancer although family members without pancreatitis also developed cancer[77] The relationship between chronic non-familial pancreatitis and pancreatic cancer is unclear. In 1950, Mikal and Campbell reported the presence of chronic pancreatitis in 49 of 100 cases of pancreatic cancer at autopsy[78]. Similarly, Gambill reported histological evidence of chronic pancreatitis in 10 per cent of 255 consecutive patients with pancreatic and periampullary cancer[79], although in an earlier study he had failed to demonstrate pancreatic cancer in 56 patients with chronic pancreatitis after 16–20 years of follow-up[80] In 1970, Robinson and colleagues were able to find only 15 authenticated cases of concurrent chronic pancreatitis and pancreatic cancer[81]. There have been other reports of pancreatic cancer developing in patients with long-standing chronic pancreatitis[82,83] but most authorities on pancreatic disease consider that the relationship is probably fortuitous[6,28]. It is possible that both diseases share common aetiologies; they certainly share the same symptom pattern and diagnostic differentiation is problematic in many cases. In addition, it is well recognized that pancreatic cancer may cause pancreatitis as a consequence of pancreatic duct obstruction[5].

Diabetes

The relationship between pancreatic cancer and diabetes mellitus has been difficult to ascertain because of problems in establishing cause and effect Medical students are taught that pancreatic cancer can worsen carbohydrate homoeostasis in established diabetics and can cause diabetes to develop *de novo*. Whether diabetes gives rise to an increased risk of developing pancreatic cancer is less clear.

The association of pancreatic cancer and diabetes was first reported before the metabolic functions of the pancreas were completely understood[84]. Since then there have been many reports of the association of the two diseases In 1941, from collected statistics, Berk reported glycosuria in 9·4 per cent of cases of pancreatic carcinoma and hyperglycaemia in 19·4 per cent[85]. Bell reported 38 cases of diabetes mellitus in 587 cases of pancreatic cancer confirmed at autopsy[86]. The incidence of diabetes in the pancreatic cancer group was twice that of the general autopsy population for men and 50 per cent greater for women. He pointed out, however, that the average duration of diabetes in the 38 pancreatic cancer cases was only 3·4 years and was less than 1 year in ten of the cases. When the 13 cases where the symptoms of pancreatic cancer antedated or coincided with the development of diabetes were excluded from the analysis, the incidence of diabetes in the pancreatic cancer group fell to that of the general autopsy population, in both men and women.

In a further autopsy study, Green and colleagues reported that 4·3 per cent of 209 pancreatic cancer patients had diabetes before the onset of the symptoms of pancreatic cancer, 15·3 per cent were found to have diabetes after the onset of such symptoms and a further 29 per cent were found to have glycosuria[87]. No conclusion was reached as to whether diabetes predisposed to pancreatic cancer. Clark and Mitchell reported on 65 patients with pancreatic cancer, ten of whom were diabetic; in all but one of these cases the interval between the diagnosis of pancreatic cancer and diabetes was less than 1 year[88]. Karmody and Kyle also found that the interval between the diagnosis of diabetes and that of pancreatic cancer was less than 1 year in 80 per cent of their 51 cases[89]. In six cases, diabetes was diagnosed more than 2 years before the development of pancreatic cancer symptoms. These authors concluded that the incidence of pancreatic cancer in such diabetics was greater than could be accounted for by chance.

The most exhaustive study of the relationship between diabetes and pancreatic cancer was published by Kessler in 1970[90]. Cancer mortality among 21 447 diabetic patients during a 26-year period ending in 1956 was reported. Male diabetics were found to have a lower than expected mortality rate from all forms of cancer while in women there was no difference from the expected rate. A statistically significant excess of deaths, in both men and women, was observed for pancreatic cancer: the standardized mortality ratio for men was 1·47 and for women was 2·13. When the deaths of patients in whom it could not be established that the diabetes had preceded the cancer were excluded from the analysis, the standardized mortality ratio fell to 1 27 for men and to 1·82 for women. This study has been criticized on the grounds that the standardized mortality ratios were calculated using data from the general Massachusetts population, which may not have been appropriate to the Boston group of patients under study. Kessler made the interesting proposition that exogenous animal insulins should be examined closely for carcinogenic effects in humans given their antigenic and teratogenic potential in animals. In a subsequent review, Kessler urged caution in the interpretation of the many reports and studies of diabetes and pancreatic cancer given the wide variation in a study design and the bias that is often present in autopsy studies[91].

Green and Jensen followed the entire insulin-dependent diabetic community in Fyn County, Denmark, for 8·5 years and reported a significant excess of pancreatic cancer cases (6 *versus* 2·4 expected) during this time[92]. When they excluded those patients in whom diabetes was probably an early manifestation of the presence of the tumour, this excess was reduced (4 *versus* 2·4 expected). They concluded that there was no association between pancreatic cancer and prior diabetes In a case–control study based on three Swedish hospitals, patients with pancreatic cancer were more likely to have diabetes than either hospital-based (relative risk 19·7) or population-based controls (relative risk 3·3)[93]. When cases where the diabetes was diagnosed less than 5 years before development of pancreatic cancer were excluded, the increased relative risk remained (6·9 compared with hospital controls, 2·4 compared with population controls) although the number of cases in each group was small.

Part of the problem in studying the link between pancreatic cancer and diabetes is a failure in most reports to distinguish between insulin-dependent and non-insulin-dependent diabetes. Endogenous insulin levels are low in the former and high in the latter. It might be postulated therefore that any increased risk of pancreatic cancer in the two subgroups should be different. Animal work has only confused the situation. Bell and Strayer demonstrated that Syrian hamsters, made diabetic by destruction of insulin-secreting islet cells by streptozotocin, do not develop pancreatic cancer when injected with carcinogen[94]. They subsequently examined the susceptibility to chemically induced pancreatic cancer in genetically diabetic and non-diabetic Chinese hamster strains and reported that tumours developed only in the non-diabetic animals[95]. In a more recent paper, Bell's group demonstrated that growth of the pancreatic cancer cell line H2T (a cancer initially induced in hamsters by the nitrosamine N-nitrosobis(2-hydroxypropyl) amine (BHP)) in hamster cheek pouches was accelerated in the presence of streptozotocin-induced diabetes[96]. No attempt was made in this latter paper to explain the seemingly anomalous results obtained.

There has been considerable interest in recent years in the relationship between pancreatic cancer and carbohydrate intolerance. In a prospective study of 99 patients suspected of having pancreatic cancer, Schwartz and colleagues measured blood glucose, serum insulin, serum C-peptide and plasma glucagon during an oral glucose tolerance test[97] They demonstrated an increased incidence of carbohydrate intolerance in the 32 patients found subsequently to have pancreatic cancer (81 per cent) compared with the 67 control patients (36 per cent), suggesting that abnormalities in carbohydrate metabolism are more widespread in patients with pancreatic cancer than had previously been realized. Insulin secretion was lower during the glucose tolerance test in the pancreatic cancer patients than in the controls. Unfortunately, the picture is again clouded in that patients with obstructive jaundice may exhibit abnormalities in carbohydrate metabolism during oral glucose tolerance tests[98].

The nature of the abnormality of carbohydrate metabolism in these patients remains unclear. While Schwartz and colleagues found low serum insulin levels in humans in response to an oral glucose tolerance test, in a recent study of pancreatic cancer induced in Syrian golden hamsters, production of insulin in response to infusions of glucose and arginine in isolated preparations of the malignant pancreas was unaffected[99].

Gallstones and cholecystectomy

In an autopsy study of 609 cases of pancreatic cancer, Bell noted that in 14 per cent of male and 38 per cent of female cases, gallstones coexisted with the tumour[86]. Despite the fact that the overall incidence of cholelithiasis in these autopsy cases (21 per cent) exceeded that of a general autopsy population, Bell concluded that there was no obvious association between pancreatic cancer and gallstones. Wynder and colleagues, in a retrospective case–control study of 142 patients with pancreatic cancer, noted a higher incidence of prior cholecystectomy in female cancer patients (15 per cent) than in controls (8 per cent), although this difference did not reach statistical significance[28]. Wynder subsequently reviewed the results of his group's initial 1973 study, and cautioned that the association between prior cholecystectomy and pancreatic cancer in women was based on a relatively small number of patients[34]. Haines and colleagues failed to demonstrate a relationship between cholecystectomy and pancreatic cancer in patients who underwent cholecystectomy more than 5 years before the development of pancreatic cancer[100]. In a review of 586 randomly selected patients with abdominal malignancy, a Finnish group suggested that there was a significantly increased frequency of prior cholecystectomy in patients developing pancreatic cancer, with the peak incidence of pancreatic cancer occurring 5 years after surgery[101].

In a small study from Athens, cholelithiasis was associated with an increased risk of pancreatic cancer (relative risk 3·5)[102]. In a more recent case–control study from Stockholm, Sweden, it was concluded that the relative risk of pancreatic cancer for subjects who reported suffering from gallstone disease was 1·7 when compared with hospital controls and 2 7 when compared with population-based controls[93]. The relative risk values were 1·2 and 2·9 after exclusion of patients who reported gallstones only in the 5 years before the diagnosis of pancreatic cancer This group concluded that the risk of pancreatic cancer was increased in patients with gallstone disease.

It has been shown, in the hamster, that cholecystectomy results in an increase in circulating plasma cholecystokinin levels, in pancreatic weight, in pancreatic DNA content and DNA synthesis rate, and in hyperplasia and hypertrophy of pancreatic cell populations[103,104]. In a Japanese study, the incidence of pancreatic cancer induced by the nitrosamine BHP was increased in animals that had undergone cholecystectomy 1 week before the first injection of carcinogen[105]. This difference did not reach statistical significance. When cholecystectomy was combined with administration of the secondary bile salt, lithocholic acid, the incidence of pancreatic carcinoma was significantly greater than in the control group which received carcinogen only.

While cholecystectomy may increase the risk of development of experimental pancreatic cancer when undertaken immediately before exposure to chemical carcinogens (the mechanism perhaps involving transient increases in cell turnover mediated by increased circulating levels of cholecystokinin), it remains to be seen whether this mechanism applies to humans who have undergone cholecystectomy many years before their presentation with pancreatic cancer Why cholelithiasis might predispose to pancreatic cancer is unclear.

Gastric surgery

In 1982, McLean-Ross and colleagues reported on the results of a follow-up study of the mortality rate and causes of death in 779 patients who had undergone peptic ulcer surgery[106]. Eighty-six per cent of the patients had undergone some form of gastrectomy and the remainder had had vagotomy and drainage. The authors found that the life expectancy of patients after peptic ulcer surgery was reduced in all age groups studied. One of the surprise findings was a statistically significant increase in the number of patients dying from pancreatic cancer (11 actual deaths compared with 3·9 expected, $P < 0{\cdot}01$). They concluded that part of this increase in the mortality rate following gastric surgery was related to continued cigarette smoking, and that this could explain the higher than expected number of patients with pancreatic cancer.

Further evidence to suggest a relationship between previous gastric surgery and pancreatic cancer was provided by Mack and colleagues[22]. In a large case–control study they demonstrated a relative risk of developing pancreatic cancer following gastric surgery (mainly partial gastrectomy) of 7·4 in non-smokers and of 8·1 for current or recent smokers (the relative risk for smokers without gastrectomy was 2·3). A threefold increase in the risk of developing pancreatic cancer following gastric surgery has been reported by other workers[107,108]. In the latter study, the relationship persisted after correction for cigarette consumption in case and control groups. This group of workers postulated that the cause for the increase in pancreatic cancer might be increased production of carcinogens such as nitrates and nitroso-related compounds in the gastric remnant. As indicated earlier, nitrosamines have been used for many years to induce pancreatic cancer in experimental animals[109]

In a follow-up study of 336 patients who underwent gastric surgery for benign peptic ulcer disease, a group from the Mayo Clinic reported no relationship between pancreatic cancer and previous gastric surgery[110]. Only one patient developed pancreatic cancer 33 years after a Billroth II subtotal gastrectomy when 1·6 cases were expected (relative risk 0·64).

Familial cases

Cases of pancreatic cancer occurring in families have appeared sporadically in the literature. For example, MacDermott and Kramer reported three brothers and one sister who all developed pancreatic cancer between the ages of 59 and 72 years[111]. Another group of four affected brothers, who all smoked cigarettes, was reported 3 years later[112]. In both of these reports, the affected individuals all developed pancreatic cancer in the high incidence age groups. Another case report published in 1977 described a father and son who presented with pancreatic cancer who had both previously been exposed to toxic chemicals[113]. There have been four other case reports of familial pancreatic cancer in the 12 years to 1987[114–117]. In 1987, one of these reports documented the familial occurrence of pancreatic cancer in three women of consecutive generations[117]. The women were European and Jewish and two died at the young ages of 29 and 42 years respectively with pathologically proven disease (the daughter and granddaughter in the series). Two of the women were smokers.

Despite these case reports, it is generally accepted that such cases are rare and that the association could still be due to chance[66].

Industrial exposure

Since Potts' original observation of an increase in the incidence of scrotal cancer amongst chimney sweeps, many investigators have looked for an association between occupational chemical exposure and human pancreatic cancer. In a study of 639 men employed in 1938 or 1939 in a company manufacturing β-naphthylamine and benzidine and followed until 1965, Mancusco and El-Attar reported six cases of pancreatic cancer[118]. These six cases accounted for almost one-third of the malignant gastrointestinal tumours recorded in the study and represented a mortality rate for pancreatic cancer in the cohort of 39 per 100 000, compared with 7·9 per 100 000 for men of similar ages in the general Ohio population.

Li and colleagues examined 3637 of 4644 death certificates of members of the American Chemical Society who died between 1948 and 1967, and compared the mortality rate from pancreatic cancer with the mortality rate of a general population of age-matched professional men[119]. They reported 56 deaths from pancreatic cancer as opposed to 35 expected deaths but were not able to implicate any one chemical substance as responsible for this increase. The authors advised caution in the interpretation of their results, given that 22 per cent of the death certificates were missing and that the relative frequency method used to make the comparisons had the potential for erroneous results. Two subsequent studies have failed to reveal such an excess of pancreatic cancer cases in chemists[120,121].

There has been one report suggesting an excess of pancreatic cancer in British radiologists but the excess was small and of marginal statistical significance[122]. In a study of 94 cases of pancreatic adenocarcinoma, lifetime occupational histories were obtained by interviewing the subjects and age-matched and sex-matched controls[70]. The proportion of male patients with pancreatic cancer who had been employed in the dry cleaning business or in jobs involving exposure to petrol was significantly higher than for male controls. The risk of pancreatic cancer was increased by a factor of five in men working in these occupations for more than 10 years.

Other workers reported as at high risk include those in the metal industry and aluminium milling, and particularly those exposed to coal tar pitch derivatives[123,124] and coke plant workers[125]. One recent letter reported the development of pancreatic cancer in a husband and wife; the husband worked in a factory making and storing chlorinated insecticides, including lindane (a possible carcinogen), and the couple lived in an apartment in the factory[126]. The authors suggested that exposure to lindane might be responsible for the development of pancreatic cancer.

Alcohol consumption

Alcohol was initially suggested as a risk factor for pancreatic cancer by Burch and Ansari in 1966[127]. In their study, 65 per cent of 83 pancreatic cancer patients admitted to moderate-to-heavy alcohol consumption for at least 15 years, compared with less than 15 per cent of the control group. Ishii and co-workers also reported that the risk of pancreatic cancer was twice as high in men who drank alcohol every day compared with non-drinkers[40]. In a case–control study, Durbec and colleagues found that the risk of pancreatic cancer increased with a high fat diet and high alcohol intake[33]. In a prospective study of 16 713 Norwegians, Heuch and co-workers found a relative risk of developing pancreatic cancer of 5·4 in individuals who consumed alcohol frequently[128].

Studies of alcoholics in many countries have failed to demonstrate a link between alcohol consumption and pancreatic cancer[129–132]. Many case–control studies have similarly failed to demonstrate any such link[22,27,28,100] while others have suggested a weak link with wine consumption in men[70].

Some authors have attempted to overcome the positive correlation between cigarette smoking and alcohol intake by attempting to standardize for tobacco use. No association between pancreatic cancer and alcohol consumption was demonstrated in the study undertaken by Wynder *et al.*[28]. In a case–control study in Baltimore, consumption of wine in both men and women even seemed to protect significantly against pancreatic cancer[45].

Despite the established relationships between alcohol consumption and cancers of the mouth, pharynx, oesophagus, larynx and liver, the link between pancreatic cancer and alcohol consumption is weak and inconsistent and suggests that any real increase in risk is likely to be small[5].

Pernicious anaemia

A Swedish group recently reported that pancreatic cancer seemed to be more common in patients with pernicious anaemia[133]. They postulated that high circulating levels of gastrin found in pernicious anaemia might exert a trophic effect on the pancreas thus increasing its susceptibility to the effects of carcinogens. They also questioned whether the production of carcinogens in the stomach through increased nitrosation might be of relevance. Interestingly, in an addendum to the paper, the authors reported an increase in plasma cholecystokinin levels in patients with pernicious anaemia compared with normal controls.

Oncogenes and pancreatic cancer

As molecular biologists and geneticists become more familiar with the human genome and techniques with which to explore it, chromosomal abnormalities associated with specific disease states are being reported with increasing frequency. This is also the case in pancreatic cancer. For example, Hirai and colleagues demonstrated that a human pancreatic cancer cell line, T3M-4, contained activated *c*-Kirsten(Ki)-*ras* oncogene[134]. Yamada and co-workers then demonstrated a point mutation at codon 12 in the same oncogene in tissue from a primary pancreatic carcinoma and in a lymph node metastasis and reported a threefold to sixfold amplification of the oncogene in both samples, suggesting that the point mutation had occurred early in the tumour process[135]. Parsa *et al.* reported the detection of *c*-Ki-*ras*-2 in 24 cases of human pancreatic cancer at a frequency of two to eight times that found in normal pancreatic tissue[136]. Almoguera and colleagues, using the technique of *in vitro* gene amplification using the polymerase chain reaction, demonstrated the presence of *c*-Ki-*ras* mutated at codon 12 in 21 of 22 human pancreatic cancers examined[137]. They concluded that this mutation was a critical event in the genesis of most human exocrine pancreatic cancers. This work was supported by the findings of Smit *et al.* who reported a similar mutation in 28 of 30 human pancreatic cancers examined[138].

As the field of molecular genetics and cancer develops, more information on the role of oncogenes in pancreatic carcinogenesis can be expected. This work should further elucidate the significance of current knowledge and may help to place some of the other putative aetiological factors into perspective.

Conclusion

There is strong evidence implicating cigarette smoking and dietary factors in the aetiology of human pancreatic cancer. The relevance of most of the other factors discussed is at best speculative and requires further investigation. Increasing knowledge of the human genome and the role of oncogenes in the carcinogenic process might provide new insight into the aetiology of this disease. Whether it offers hope for prevention or cure remains to be seen.

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Abdominal wall pain: an alternative diagnosis

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The cause of abdominal pain need not necessarily reside in the viscera; the abdominal wall is another source of symptoms. Some causes of abdominal wall pain are obvious, e.g. hernias, but not so others such as nerve entrapment syndromes. This review is concerned with causes of abdominal wall pain which, although common, may be easily overlooked.

Keywords: Abdominal pain, diagnosis

The patient with chronic abdominal pain constitutes a common medical and surgical problem; despite the variety of tests available the cause often remains elusive. Failure to make a prompt diagnosis is not only vexing for the clinician, but also it can condemn the patient to a series of uncomfortable and unrewarding investigations. The position was made clear by Hutchinson: 'In the treatment of the chronic abdomen the most important thing is to catch the patient early. If she has once set her feet on the slippery slope which leads to successive operations she is undone'[1].

The reasons why some cases of abdominal pain are hard to diagnose are that pain is subjective and our understanding of the mechanisms of visceral nociception is poor. As a result, difficulty is experienced by patients in describing their pain and by doctors in deciding on its likely origin. Most patients presenting with chronic abdominal pain are assumed to have visceral disease. However, if after investigation no such cause is found, refuge may be sought in other less well defined diagnoses such as functional or psychiatric disorders Before these alternatives are pursued it should be remembered that abdominal pain can arise not only from the viscera but also from the abdominal wall tissues, namely the skin, subcutaneous fat, muscle, bone and parietal peritoneum[2].

There are many causes of abdominal wall pain. Some, by virtue of the physical signs which they produce, are obvious, e.g. hernias or shingles; others require a more discriminating approach, e.g. the myofascial pain syndromes. The aim of this review is to show how certain parietal lesions can trap the unwary clinician into making a misdiagnosis of visceral disease; it then goes on to describe a practical approach to their elucidation.

Perception of visceral pain

The ability to define the site of a noxious stimulus becomes increasingly difficult as one passes through the deep tissues to the viscera'[3]. In contrast to the epicritic pain of cutaneous lesions, visceral and muscular conditions produce a dull aching pain which is felt more diffusely. At these deeper levels the site of the pain no longer provides an accurate guide to its origin.

In 1893 Head first used the term 'referred pain' and defined it as the 'somatic localization of sensory experiences evoked from the viscera'[4]. Although the physiological mechanisms responsible are still incompletely understood it is the phenomenon of referred pain which provides the key to an understanding of why parietal and visceral pain may be confused. Referred abdominal pain results from the integration of nervous impulses arising in the two main divisions of the nervous system. The autonomic system provides visceral pain afferents via the sympathetic nerves and the somatic nervous system supplies the anterior abdominal wall with sensation via the lower six intercostal nerves.

Under normal physiological circumstances we are unaware of our viscera and remain so until an appropriate stimulus is applied[5]. When the stimulus is sufficiently great, pain is felt However, since the viscera are not represented at a conscious level the pain cannot be localized to a particular organ, and is instead referred to the surface of the abdomen, to an area innervated by the same spinal cord segments which serve the affected viscus.

The neural pathways responsible for referred pain have not yet been clearly defined, but as a proposed mechanism the projection–convergence theory has received some experimental support[6]. This postulates that visceral pain afferents entering the spinal cord converge with cutaneous pain afferents to end on a common neuron. The brain then interprets impulses reaching the common pathway as having come from the skin, since previous experience will have conditioned it to believe that the common tract was initially stimulated by cutaneous afferents. The spinothalamic tract appears to be the most likely site for visceral and cutaneous afferents to converge.

Just as the brain may misconstrue the true origin of nervous traffic reaching it along the common pathway, so the clinician may also misinterpret parietal pain as having its origin in visceral disease. But is there any evidence to suggest that abdominal wall pain is clinically important? The evidence is presented below.

Abdominal wall pain

The first clear description of abdominal pain originating from structures other than the viscera was provided by Cyriax in 1919[7]. Through his clinical practice he became convinced that in a number of cases 'the diagnosis of referred pain of visceral disease is erroneous'. He considered that such pains could be mimicked by lesions which affected the vertebrae, ribs or their associated muscles, or that they were the result of direct irritation of nerves in the intercostal spaces By identifying such conditions as alterations in the normal vertebral curves, minor subluxation of vertebral bodies, and pressure on the peripheral portions of intercostal nerves, he was able to employ various mechanical treatments to correct the abnormalities and relieve his patients' symptoms.

Despite Cyriax's work little attention was paid to the identification of parietal lesions until the observations of Carnett in 1926[8] Carnett recognized the diagnostic problems posed by abdominal wall lesions and maintained that abdominal pain could be caused by neuralgia affecting one or more of the lower six intercostal nerves. To distinguish this condition from intra-abdominal diseases he developed a simple test which, when positive, localized the origin of symptoms to the parietes rather than the viscera

Carnett's test

The abdomen of the supine patient is palpated in the usual way to elicit the area of tenderness. Then, with the palpating fingers still located over the tender spot, the patient is asked to contract

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the abdominal muscles by raising the head from the couch. Once the muscles are tensed, pressure is reapplied and the patient asked if the pain has altered. If the cause of symptoms is intra-abdominal, the tensed muscles now protect the viscera and the tenderness should diminish. On the other hand, if the source resides in the abdominal wall the pain will be at least as severe, and even increased.

Although Carnett's test made it possible to distinguish between visceral and parietal pain, there was still no evidence to suggest that such lesions could produce pain which was of a similar nature to that of visceral disease. It was not until the 1940s that such proof was forthcoming through the experimental work of Lewis and Kellgren: By injecting hypertonic saline into the interspinous ligaments, these workers were able not only to reproduce the segmental pattern of referred pain but also other manifestations associated with visceral disease[3]. For example, by injecting the interspinous ligament at the level of the first lumbar vertebra, pain could be produced which was both similar to that of renal colic and associated with the same somatic reflexes, such as muscular rigidity and retraction of the testis. From this and other experiments Lewis concluded that all the features which we normally attribute to painful visceral disease could be derived from somatic structures lying in the appropriate dermatome.

Clinical studies have been carried out to assess the value of diagnosing abdominal wall pain in managing patients with both acute and chronic abdominal symptoms. Mehta and Ranger identified 103 patients as having parietal pain by the demonstration of 'trigger points' sited along the lateral border of the rectus muscle[9]. With injections of 5 per cent aqueous phenol into these points they were able to produce long-term pain relief in 56 per cent of their patients. Similarly other authors have reported on the efficacy of injecting the parietes to relieve chronic abdominal symptoms[10–12] and, in our own series, we demonstrated that 22 of 26 patients were cured by such treatment[13].

Thomson and Francis looked at the value of finding abdominal wall tenderness in patients presenting with an acute abdomen[14] Of 120 patients, 24 were thought to have symptoms originating in the parietes. Eleven of these patients nevertheless underwent operation because of the overall clinical picture, but in only one case was an intra-abdominal lesion found to account for the pain All the remaining 96 patients, with no sign of abdominal wall tenderness, proved to have a definite intra-abdominal disease. Gray *et al* have also reported on the presence of abdominal wall tenderness in patients with a diagnosis of non-specific abdominal pain and found it to be present in 28 per cent[15]

Causes of abdominal wall pain

Iatrogenic peripheral nerve injuries

One of the commonest causes of abdominal wall pain is a prior surgical procedure[16,17]. Abdominal scars are usually symptom-free, but where the incision directly involves a cutaneous nerve, subsequent entrapment of that nerve may occur either in a suture or in later scar formation The ilioinguinal and iliohypogastric nerves are particularly at risk in lower abdominal incisions. In addition to Carnett's test, the following triad is diagnostic. (1) burning or shooting pains in the area supplied by the nerve; (2) impaired sensory function in the distribution of the nerve; and (3) relief of pain by infiltration with local anaesthetic[16]. Once recognized, treatment may be by local injection of steroids, local anaesthetic or 5 per cent phenol. Accurate placement of the injection is of paramount importance and may be improved by the use of a nerve stimulator[18]. Should these measures fail then exploration of the scar should be considered. the involved nerve is traced laterally to where it leaves the retroperitoneum, and sectioned. The subsequent neuroma which forms generally produces no pain at this point.

Abdominal cutaneous nerve entrapment

A nerve entrapment syndrome may occur without prior surgical damage Applegate has described well localized areas of abdominal tenderness lying along the lateral margin of the rectus muscle[10]. He suggests that such areas are produced at sites where the anterior cutaneous branch of an intercostal nerve passes through the rectus muscle to pierce its anterior sheath; in this position it may become intermittently compressed producing pain which may mimic that normally associated with conditions such as biliary or renal colic. Of 62 patients identified as suffering from the syndrome all but one obtained relief with local anaesthetic injection. The one patient who failed to respond was subsequently cured by section of the relevant nerve as it emerged from the rectus muscle.

Hernias

The majority of abdominal wall hernias are apparent on clinical examination, the presence of a lump with an expansile cough impulse serving to make the diagnosis. However, some hernias elude detection, either because they are small or because the patient is obese. In cases where the diagnosis is suspected but clinically unconfirmed, additional investigation using radiography or ultrasonography may be helpful. Thus herniography, in which contrast medium is introduced into the peritoneal cavity, has been successfully used to reveal previously undetected inguinal hernias in patients with groin pain of uncertain origin[19,20] and to detect impalpable interparietal lesions such as Spigelian hernias[21].

Myofascial pain syndromes

This group of syndromes is now well described but they continue to go unrecognized and remain poorly understood. In the past they have been referred to by a variety of terms including muscular rheumatism, myalgia and fibrositis[22].

The syndromes arise from the presence of trigger points in muscles or fascia; such points are usually the result of antecedent trauma, and activity within them produces pain which may occur, for example, during muscle contraction. Diagnosis relies on finding the trigger spot, either by palpation or by eliciting certain physical signs such as a taut band of muscle fibres or a localized twitch response when the involved part of the muscle is pinched[23].

Treatment again rests on the accurate injection of local anaesthetic solution into the affected area. In some patients several such areas may be present and require treatment[24].

The rib tip syndrome

This syndrome, characterized by pain along the costal margin, is generated by the hypermobility of the eighth, ninth and tenth ribs[25]. These ribs do not articulate with the sternum but instead are bound to each other by a thin band of fibrous tissue. Should this fibrous attachment be divided, the rib may ride up and irritate the intercostal nerve to produce pain. The patient may be aware of a snapping or clicking sensation as the ribs move relative to one another and the clinician can reproduce the symptoms by hooking his or her fingers under the costal margin and pulling upwards. Relief can be provided by anaesthetizing the relevant intercostal nerve with local anaesthetic but where symptoms persist rib tip resection may be necessary.

Abdominal pain of spinal origin

The complex arrangement of the musculoskeletal structures which make up the vertebral column and the close relationship which these bear to the nerve roots can produce a variety of neurological symptoms. When the normal anatomy is disturbed in such a way that the roots of the intercostal nerves are irritated, abdominal pain may result. In some cases the spinal origin of the pain will be made obvious by additional symptoms and signs but in many patients with only minor degenerative disease the true aetiology may escape identification. The

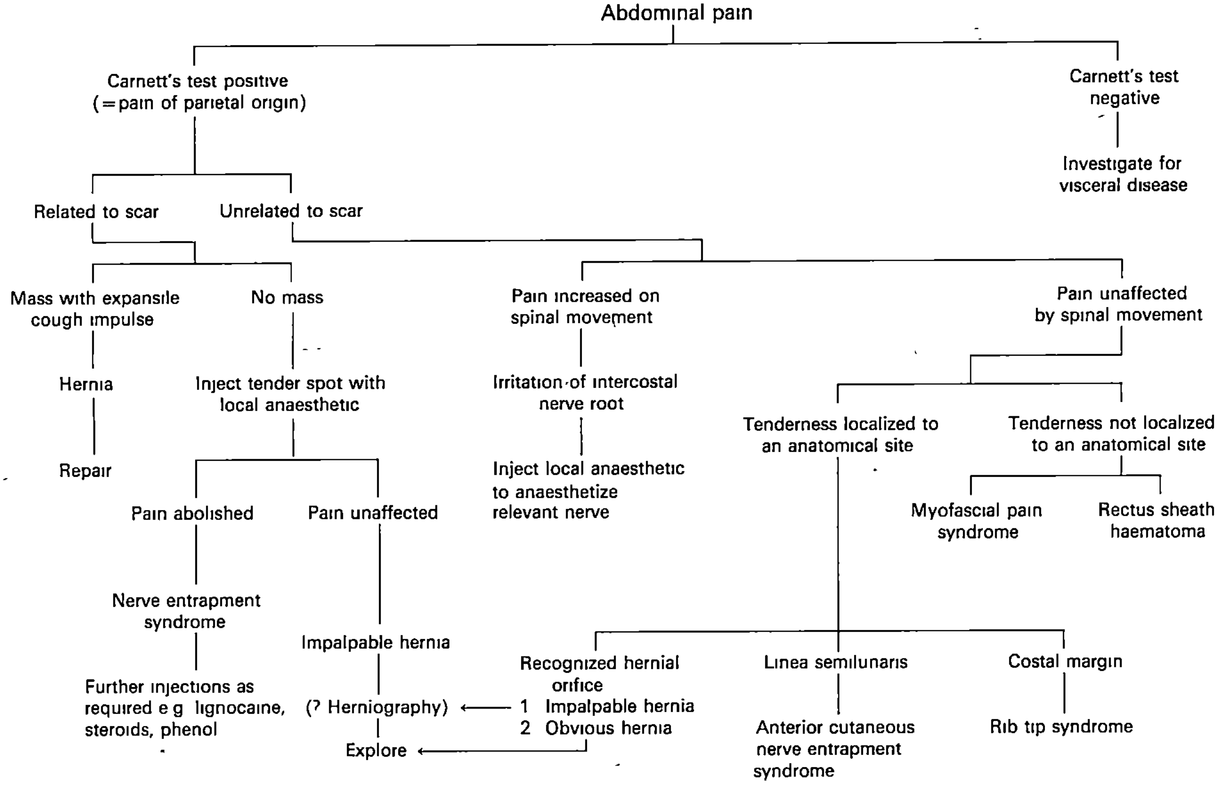
Abdominal pain
Carnett's test positive
(=pain of parietal origin)
Carnett's test negative
Investigate for visceral disease
Related to scar
Unrelated to scar
Mass with expansile cough impulse
No mass
Pain increased on spinal movement
Pain unaffected by spinal movement
Hernia
Inject tender spot with local anaesthetic
Irritation of intercostal nerve root
Tenderness localized to an anatomical site
Tenderness not localized to an anatomical site
Repair
Inject local anaesthetic to anaesthetize relevant nerve
Pain abolished
Pain unaffected
Myofascial pain syndrome
Rectus sheath haematoma
Nerve entrapment syndrome
Impalpable hernia
Recognized hernial orifice
Linea semilunaris
Costal margin
Further injections as required e g lignocaine, steroids, phenol
(? Herniography)
1 Impalpable hernia
2 Obvious hernia
Explore
Anterior cutaneous nerve entrapment syndrome
Rib tip syndrome

Figure 1 *An approach to the diagnosis and management of abdominal wall pain*

diagnosis may be suspected by finding that the pain is aggravated by certain postures, by eliciting tenderness at the site of the pain, which is increased by muscle contraction, and by observing posterior intercostal tenderness in the region of the vertebral transverse processes. In a series of 73 patients, provisionally diagnosed as having pain of spinal origin, the diagnosis was confirmed in 53 (73 per cent) patients, of whom 49 received intercostal nerve blocks with the result that 33 (67 per cent) patients were rendered pain-free for at least 3 months[26]

Spontaneous rectus sheath haematoma

This is a well described, though frequently missed, condition resulting from rupture of the epigastric vessels. The patient usually presents suddenly with well localized abdominal pain associated with a tender non-pulsatile abdominal mass, usually in the lower abdomen[27]. There is frequently a plausible precipitating factor such as local trauma, a bout of coughing, or anticoagulant therapy. The diagnosis can be confirmed on ultrasound examination and a conservative approach to treatment can be adopted provided the haematoma does not enlarge[28].

The clinical approach

Figure 1 sets out an algorithmic approach to the diagnosis of abdominal wall pain. Although Carnett's test provides objective evidence of the diagnosis the condition can often be suspected from features in the history. A relationship to abdominal surgery, damage to muscle fibres following physical exertion, or a long and fruitless search for visceral disease all suggest consideration of the diagnosis, while coughing, turning over in bed or the lifting of heavy weights (as in women carrying their weekly shopping) may all increase tension in affected muscle groups and hence the discomfort.

Despite the demonstrated efficacy of diagnosing abdominal wall pain, an important caveat must be added. Where, despite a positive Carnett's test, the overall clinical picture suggests a more serious underlying pathology it is encumbent upon the clinician to exclude it; false positive results can undoubtedly occur.

Conclusion

The diagnosis of patients with chronic abdominal pain can be a difficult and time-consuming task even with modern investigative techniques; early consideration should be given to the abdominal wall as a source of symptoms in all such cases. The accurate diagnosis of abdominal wall pain can lead to effective treatment.

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Parathyroid autotransplantation

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This paper reviews the technique, indications and results of parathyroid autotransplantation. Autotransplantation is most commonly indicated following parathyroidectomy for renal osteodystrophy, but can also be used in primary hyperplastic hyperparathyroidism, re-exploration of the neck and radical neck surgery. The success of the technique ranges from 75 to 100 per cent.

Keywords: Parathyroid glands, autologous transplantation, renal osteodystrophy, hyperparathyroidism.

Even for experienced endocrine surgeons, re-exploration of the neck to remove parathyroid tissue in the face of persistent or recurrent hyperparathyroidism is a difficult task and the chances of achieving normocalcaemia after such surgery are low. The complications of parathyroid surgery, particularly recurrent laryngeal nerve palsy, are also more frequent following re-exploration. For these reasons, a technique for the management of disease of all the parathyroids which involves total excision of all parathyroid tissue from the neck at initial exploration has considerable appeal. Reimplantation of some of the parathyroid tissue at a more accessible site allows near normal parathyroid function to be regained and facilitates exploration should this become necessary. This manoeuvre is generally termed 'autotransplantation'.

History

Parathyroid autotransplantation has been performed since the latter part of the last century, but Halsted[1] was one of the first to experiment with the technique successfully, demonstrating that tetany after total parathyroidectomy could be prevented in dogs by reimplantation of excised parathyroid tissue. Lahey was the first to perform this procedure in man[2], followed closely by Cattell[3]. In 1967, Fisher *et al.*[4] could not achieve successful autotransplantation in dogs and concluded that it did not have a role to play. Others, none the less, started performing the operation in man[5], and interest in the technique was then renewed by Wells *et al.* in 1975 when they performed a series of 29 parathyroid autotransplants in man, with a graft survival rate of 93 per cent.

Indications

Although the viability of the technique is well established, the indications for its use are still controversial. There are four groups of patients in which parathyroid autotransplantation may be considered.

Patients with renal disease (renal osteodystrophy)

The commonest indication for autotransplantation is in the treatment of secondary or tertiary hyperparathyroidism in renal disease[6–12]. Such patients are usually in end-stage renal failure and are maintained on dialysis, or have had a renal transplant. The glands become hyperplastic to compensate for abnormal calcium, phosphate and vitamin D metabolism. Calcium regulation is maintained but in tertiary hyperparathyroidism the glands may eventually become autonomous, resulting in hypercalcaemia or osteodystrophy. If parathyroidectomy is performed for secondary hyperparathyroidism, parathyroid tissue left in the neck to prevent subsequent hypoparathyroidism may be subject to further stimulation as the underlying renal disease is usually irreversible; this results in tertiary hyperparathyroidism. In tertiary hyperparathyroidism, regrowth and recurrent hypercalcaemia commonly occur[10] because of the neoplastic nature of the tissue. Recurrent hyperparathyroidism usually necessitates re-exploration of the neck, which may be hazardous. Therefore, it has been considered safer to perform total parathyroidectomy and to transplant parathyroid tissue to a site that is easy and safe to explore should hyperparathyroidism recur. This option appears to be satisfactory in both children[13] and adults.

The reported incidence of recurrent hyperparathyroidism after subtotal parathyroidectomy in various series ranges from 8 to 40 per cent[10,14,15]. After total parathyroidectomy and autotransplantation the incidence of recurrence is generally lower, but reported rates range from zero to 6 per cent[10,16], with an incidence of hypocalcaemia ranging from zero to 7·7 per cent (failed parathyroid autotransplantation)[5,14,16,17]. A higher incidence of hypocalcaemia is reported by some (27–31 per cent)[15,18], but this is unusual, In one study the incidence of recurrent (graft-derived) hypercalcaemia was 25 per cent[14], but in other series this problem was not seen[12]. Others[8], however, have found difficulty in treating recurrent hypercalcaemia by excising part of the transplanted parathyroid tissue and do not recommend autotransplantation in renal disease. Yet others[19] have treated patients successfully by subtotal parathyroidectomy and do not recommend parathyroidectomy and parathyroid autotransplantation, but they are in a minority.

There is thus a good case for total parathyroidectomy with autotransplantation in the management of renal osteodystrophy, but the benefits are neither predictable nor guaranteed.

Primary hyperparathyroidism

Parathyroid autotransplantation is not indicated in primary hyperparathyroidism due to adenoma or carcinoma as only one gland need be removed in these cases[10]. The value of autotransplantation in primary hyperplastic hyperparathyroidism is not well established[20]. The incidence of recurrent hyperparathyroidism following a standard subtotal parathyroidectomy for primary hyperplastic hyperparathyroidism, in which three-and-a-half glands are removed, is low (zero–18 per cent)[10,21–24], and most studies do not recommend treatment by total parathyroidectomy and autotransplantation. Higher incidences of recurrence (33–100 per cent) are none the less reported[25,26]. Similarly, the incidence of hypocalcaemia is low (1–15 per cent)[10,23,27], although once again higher figures have been reported (27–30 per cent)[10,28]. Where a high incidence of recurrent hyperparathyroidism after subtotal parathyroidectomy has been noted, authors tend to recommend total parathyroidectomy and autotransplantation for primary hyperparathyroidism as well[9,29,30]. In one case this procedure was successful in an infant under 2 years of age, in which case reoperation on the neck would be particularly hazardous[31].

The balance of opinion is, however, against the use of total

0007-1323/90/101171-04

parathyroidectomy and autotransplantation for primary hyperparathyroidism.

Failed initial partial parathyroidectomy

Autotransplantation may be indicated after re-exploration of the neck for either recurrent primary hyperparathyroidism or hyperparathyroidism due to adenoma or carcinoma[7,9,32–34].

In recurrent hyperparathyroidism, the remaining parathyroid tissue may be damaged or devascularized at re-exploration, and subsequent hypocalcaemia is common (19–37 per cent)[10,35–39]. In these cases, parathyroid autotransplantation may prevent hypoparathyroidism.

Normal retained parathyroid glands may be damaged when the neck is explored again to search for a previously undiscovered adenoma, and removal of the adenoma may thus render the patient hypocalcaemic. Autotransplantation of a portion of the adenoma may be performed to avoid this[40] The disadvantage of this procedure is that the transplanted adenomatous tissue may continue to excrete excess parathormone, resulting in an unacceptably high incidence of recurrent hyperparathyroidism[32,41–43]. Testing for autonomy may be performed on cryopreserved tissue before autotransplantation. A carcinoma should obviously not be transplanted[44], but a proportion of residual normal gland may be.

It is essential to be sure that there is no residual parathyroid tissue in the neck, such as a fifth gland[7], before parathyroid autotransplantation is performed after reoperation of the neck. If doubt exists that unidentified parathyroid tissue persists in the neck, excised parathyroid tissue may be cryopreserved rather than transplanted, and transplanted at a later date if necessary[10,45]. Immediate autotransplantation should only be performed when the surgeon is confident that all parathyroid tissue has been removed from the neck

Radical neck dissection

The final indication for parathyroid autotransplantation is after radical neck dissection[46,47] in, for example, thyroid malignancies[7,48–51], when hypoparathyroidism occurs in 3–70 per cent of cases[50,52–57], or at laryngectomy for carcinoma[45,54]. Autotransplantation has also been advocated at thyroidectomy for Graves' disease[3] if the parathyroid glands are inadvertently excised with the thyroid. Occasional reports of a high late incidence of hypocalcaemia (38 per cent)[48] are the exception and, in the hands of most surgeons, the incidence of this complication is low (1–9 per cent)[10,50,53,57–60], and parathyroid autotransplantation is not normally necessary. There were no cases of hypocalcaemia reported in one series, however, in which autotransplantation was performed into sternomastoid muscle[50] It is therefore a good discipline to inspect all thyroidectomy specimens before they leave the operating field, and reimplant any retained parathyroid glands into the sternomastoid. The need for re-exploration of the neck for hyperparathyroidism is not a risk for these patients[32,61] as there is no stimulus for the transplant to become autonomous, although further neck surgery may sometimes be required for other reasons.

Technique

The most widely used technique is that described by Wells *et al.*[45]. Parathyroid tissue is placed in saline at 4°C or in tissue culture medium as soon as possible after excision, and a portion is examined histologically by frozen section to ensure that the tissue transplanted is of parathyroid origin[2]. The most normal looking parathyroid tissue, judged macroscopically or microscopically, is used and obvious microadenomata avoided if possible. After cooling for 30 min, the glands are sufficiently firm to be sliced and the chosen fragment is cut into 1 mm slices or 1 × 1 × 2 mm cubes on a wooden block using a scalpel. A 5 mm cube of parathyroid tissue is usually sufficient to provide enough material for transplantation.

The parathyroid tissue is usually implanted in the brachioradialis muscle of the forearm[9,45,62] This is the most convenient place for subsequent exploration and allows differential parathormone assays in the venous blood of each arm to assess graft function. Care is taken to avoid an arm with an arteriovenous fistula that is being used or may be used for haemodialysis. The forearm is prepared while the neck is explored. A vertical incision is made over the flexor muscles and the deep fascia exposed. Several spaces are made in the muscle by blunt dissection and a piece of parathyroid tissue inserted into each. The incision is closed with a non-absorbable suture or clip to assist subsequent localization. Generally, 10–20 pieces are inserted[9,32,45,62], although half that number[63] or even as little as five fragments[64] have been used. Necrosis of the cells at the centre of $1\ mm^3$ cubes has been reported at subsequent histological examination, and smaller pieces may be ideal[10,65]. The remaining pieces are cryopreserved[9,45,62] if facilities are available. In the postoperative period the arm should not be used for blood pressure measurements or venesection[45]

Other implantation sites, such as the sternocleidomastoid[5,49,66,67], thigh muscles[47,67], and trapezius or pectoralis muscles[54], have been used, but re-exploration of these sites is more difficult. Implantation of slices or cubes is time-consuming and an alternative technique which may be quicker and improve graft viability is the injection of a suspension of parathyroid tissue in saline into the forearm[68,69]. This technique must not be used when there may be a need for subsequent excision of part of the graft, as injected parathyroid tissue is diffuse and difficult to localize for re-excision

Success of parathyroid autotransplantation

Transplants take some time to come into effect and, without support by synthetic vitamin D and calcium supplements, profound hypocalcaemia will be experienced until the transplanted fragments have grown This is a particular problem in patients with long standing severe hypercalcaemia with bone damage. Reversal of this may lead to 'hungry bones' which make an excessive demand on available calcium[10]. The time between autotransplantation and withdrawal of pharmacological support to maintain calcium balance varies from a few weeks to 6–12 months in different series[12,40] Functional recovery of transplanted parathyroid tissue may take place over several weeks[62,70] up to 12 months[63] This lull in parathyroid activity can be controlled in renal patients by alterations in dialysate calcium concentrations. There is evidence of graft survival in 75–100 per cent of parathyroid transplants[5,9,12,17,32,40,45,47,49,61,71]. However, the success of removal of fragments if hyperparathyroidism recurs is variable[8,30,41]. The grafts are said to be functioning if the parathormone level is one or two times higher in the antecubital vein of the transplanted arm when compared with the other arm[32,72,73], or if the patient remains normocalcaemic without pharmacological support[32,45]. Systemic hypercalcaemia does not inhibit the establishment of a viable graft, although parathormone secretion from the graft may be suppressed[70].

It may be that transplanted tissue does not work as well as normal tissue, and supplementary calcium may be needed in times of stress such as pregnancy[67]. The incidence of latent hypoparathyroidism, as this is called, has been reported to be as high as 19 per cent[18]. Late failure of the graft has also been reported[10].

The incidence of overgrowth of the graft with early recurrence of hypercalcaemia (graft-dependent hypercalcaemia), is reported as between zero and 15 per cent[5,11,12,16–18,45,71,74]. Difficulty in localizing the implant may occur, especially following injection of parathyroid suspensions, and migration of parathyroid tissue into the lymphatics may give enlarged axillary deposits of parathyroid tissue. Difficulty in calculating the amount of transplanted tissue on re-exploration is described[41,42], although other authors have not found this to be a problem[9,12,45]

Cryopreservation

This technique is becoming increasingly popular. Parathyroid tissue is not transplanted immediately after excision, but, after slicing, is frozen in liquid nitrogen at a rate of -1°C per min to -200°C for storage[45]. Dimethylsulphoxide is added as a cryopreservative[75] in a 10 per cent solution with 10 per cent human serum and 80 per cent tissue culture medium[45]. The tissue is thawed immediately before implantation and washed twice in tissue culture medium to remove the dimethylsulphoxide.

Graft survival in immediate parathyroid autotransplantation after cryopreservation was similar in rats after 10 days[76], with a success rate of 80 per cent at 9 months[77]. A 71 per cent success rate ('take') has been described in dogs after 2 months[78]. In man, cryopreserved tissue has been used up to 18 months after excision[79] with a 'take' rate of 66 per cent.

If there is doubt whether the cryopreserved tissue will assume autonomous unsuppressed secretion of parathormone after implantation, an *in vitro* suppression test can be performed[7] by measuring the parathormone output in the presence of increasing ambient calcium concentrations. Delay in implantation allows accurate postparathyroidectomy assessment of the need for autotransplantation.

Cryopreservation has not been widely accepted, as the technique is difficult and the equipment necessary is not widely available. Nevertheless, the use of cryopreserved tissue allows precise evaluation of the need for autotransplantation[32,40,64] and may be particularly valuable when the surgeon is uncertain of the degree of clearance of parathyroid tissue from the neck. The ability to perform a functional assessment of the parathyroid tissue before reimplantation may become increasingly important in patients with tertiary hyperparathyroidism or adenomata.

Conclusions

There have been no randomized controlled comparisons of the value of total parathyroidectomy and autotransplantation as opposed to subtotal parathyroidectomy[10,73]. It is therefore difficult to compare these two forms of treatment objectively. Others have compared different surgical procedures without separating the underlying pathological conditions[80]. In particular, outcome should be assessed with regard to: (1) success in control of hypercalcaemia; (2) duration of this control, if achieved; (3) incidence of hypocalcaemia; and (4) ease of treatment of subsequent recurrence. The balance of evidence would, however, favour the retention of a three-and-a-half gland parathyroidectomy in all initial explorations of patients with primary hyperplasia. Parathyroid autotransplantation should probably be reserved for those patients undergoing reoperation for recurrent disease and for those with tertiary hyperparathyroidism on renal replacement therapy. Cryopreservation cannot be universally recommended as the specialized expertise and required facilities are not widely available.

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Surgery in patients on long-term steroid therapy: a tentative model for risk assessment

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Increased morbidity after operation has been associated with long-term steroid therapy. To determine the correlation between steroid therapy and such morbidity, the perioperative course of 55 steroid-treated patients was reviewed: 27 had bronchopulmonary disorders (group P) and 28 had non-pulmonary diseases (group NP). There were six (11 per cent) deaths, of which three were steroid related. Among the 13 non-lethal postoperative complications, eight were considered to be steroid related in group P and one in group NP. The duration of steroid therapy was for a median of 24 months (range 1–408 months) in group P and for a median of 6 months (range 1–240 months) in group NP ($P < 0.01$). *In contrast, the daily dose of hydrocortisone or equivalent before operation was significantly lower in group P, with a median of* $0.51\ mg\ kg^{-1}\ day^{-1}$ *(range* $0.20–2.56\ mg\ kg^{-1}\ day^{-1}$*) than in group NP, with a median of* $1.20\ mg\ kg^{-1}\ day^{-1}$ *(range* $0.23–7.38\ mg\ kg^{-1}\ day^{-1}$*)* ($P < 0.01$). *In conclusion, bronchopulmonary disorders requiring a long duration of steroid therapy are associated with a higher risk of steroid-related complications after surgery. A convenient mathematical model is proposed which may allow a preoperative assessment of surgical risk, using steroid dose and duration of treatment.*

Keywords: Obstructive lung disease, operative surgery, pituitary–adrenal system, probability, steroids

Long-term steroid therapy in surgical patients has been associated with an increased perioperative risk of developing complications related to inhibition of the hypothalamic–pituitary–adrenal axis. This inhibition causes not only an insufficient response to stress but also an impairment of tissue healing and a variety of endocrine and metabolic side-effects, including increased susceptibility to infection[1–3]. The physical status classification of the American Society of Anesthesiologists (ASA)[4], the Goldman cardiac risk index (CRI)[5] and the acute physiology score (APS)[6,7] do not include steroid therapy as a specific risk factor. Steroid impregnation and the related side-effects depend largely on dose and duration of therapy as well as on the nature and severity of the underlying disease. There is considerable individual variation. So far little has been written about the correlation between morbidity after surgery and the level of steroid impregnation.

This paper reviews a personal experience of postoperative complications in steroid-treated patients. A tentative model, using dose and duration of steroid therapy before operation as parameters of steroid impregnation, is proposed which may allow a convenient preoperative classification of surgical risk in such patients.

Patients and methods

Patients

Between February 1982 and December 1989, 55 steroid-treated patients had a total of 55 surgical procedures. There were 32 men and 23 women of mean(s.d.) age 57(17) years (median 61 years, range 21–87 years). Forty patients had intraperitoneal operations (splenectomy, seven; complicated duodenal ulcer surgery, four; cholecystectomy, five; Nissen fundoplication, one; ileal resection, four; colonic surgery, 17; Puestow procedure, two). Fifteen patients had extraperitoneal surgery (Patey mastectomy, one; thyroidectomy, two; umbilical or inguinal hernia, 11, radical nephrectomy, one). There were 24 (44%) emergency operations, nine of which were for acute complications related in part to steroid treatment (bleeding ulcer, three; perforated duodenal ulcer, one; sigmoid perforation, five) Seven operations were performed under spinal anaesthesia and 48 under general anaesthesia.

Steroid therapy

The indications for steroid treatment are detailed in *Table 1*. All 55 patients were receiving long-term steroids at the time of surgery; the median duration of therapy was 18 months (range 1–408 months) All patients received daily oral ($n = 51$) or intravenous ($n = 4$) steroids. Preoperative steroid dose was expressed as the daily dose of hydrocortisone, or the equivalent hydrocortisone dose if a synthetic analogue was used, during the last month before surgery. The median preoperative steroid dose was 51 mg day^{-1} (range 15–480 mg day^{-1}). Replacement therapy in primary chronic adrenal insufficiency or very short-term steroid treatment for conditions such as septic shock was not included in the study. The features of long-term steroid administration were present in many patients (Cushingoid appearance, 12; osteoporosis, 20, diffuse ecchymoses, 13; myopathy, eight; history of poor wound healing or susceptibility to infection, 14; peptic ulcer disease, ten; impaired glucose tolerance, 19).

Perioperative management

For elective surgery, attempts were made to reduce the preoperative steroid dose, especially in haematological disorders which were usually treated with short-term high-dose therapy Elective patients had respiratory preparation with incentive spirometry[8]. Appropriate supplementary hydrocortisone hemisuccinate was given intramuscularly with premedication, and the same drug was used intravenously during and in the early period after surgery The dose was gradually reduced within 2–7 days[3]. All patients received at least short-term prophylactic antibiotics. In some cases a 7–10-day course of antibiotics was justified. Precautions concerning the abdominal wound were taken, including interrupted absorbable aponeurotic sutures, an elastic abdominal girdle, and delayed removal of skin stitches (3 weeks) One author (L.A.M.) was involved with the operative and perioperative management of all patients.

Risk factor assessment

The preoperative condition of each patient was assessed using the ASA classification[4] and Goldman's CRI[5]. To analyse the steroid

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Table 1 *Indications for long-term steroid administration in 55 patients*

Indication	n
Bronchopulmonary diseases (49%)	
Chronic obstructive airways disease	23
Atopic asthma	4
Haematological disorders (22%)	
Idiopathic thrombocytopenic purpura	6
Chronic lymphocytic leukaemia	4
Non-Hodgkin's lymphoma	1
Waldenström's macroglobulinaemia	1
Miscellaneous (29%)	
Regional enteritis (Crohn's disease)	6
Pemphigus vulgaris	1
Rheumatoid arthritis	7
Intracranial hypertension (metastatic carcinoma)	2

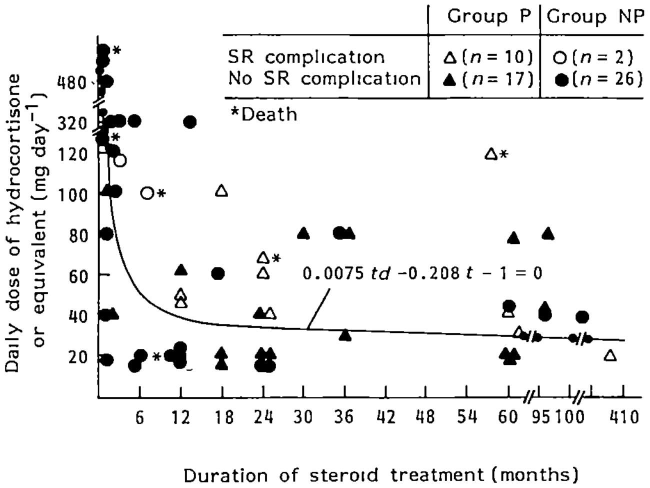

Figure 1 *Total duration (months) of steroid therapy*, t (x *axis*) versus *dose* (*mg day*$^{-1}$) *of hydrocortisone or equivalent during the last month before surgery*, d, (y *axis*) *The hyperbolic curve shows an estimated relationship between the variables* t *and* d *and is derived from the data of Kehlet and Binder*[9] *SR, steroid-related*

impregnation of patients two parameters were used total duration of steroid therapy in months (t) and daily dose of hydrocortisone in mg day^{-1} during the last month before surgery (d) Data from Kehlet and Binder[9] allowed a relationship to be derived between these variables t and d The following is an equivalence equation of a hyperbolic curve[10]:

$$0\cdot0075td-0\cdot208t-1=0$$

According to this tentative mathematical relationship, each point on the curve corresponds to an equivalent steroid impregnation (*Figure 1*) Patients' data were plotted on the graph and location above (high impregnation) or below (low impregnation) the hyperbolic curve was recorded for subsequent analysis

Steroid-related complications

Steroid-related complications after surgery were defined as: (1) an episode of adrenal insufficiency due to impairment of the hypothalamic–pituitary–adrenal axis; (2) problems due to altered tissue healing such as dehiscence, incisional hernia, hernia recurrence, etc., and those of increased tissue fragility and susceptibility to infection, (3) perioperative upset in steroid therapy leading to complications related to the underlying steroid-treated disease, especially bronchopulmonary disease

Statistical analysis

Non-parametric methods were used. Wilcoxon's rank sum test for numerical variables and Fisher's exact test for categorical variables

Results

Six of the 55 patients died, giving a hospital mortality rate of 11 per cent; three deaths were steroid related. All six died after emergency surgery for which the mortality rate was 25 per cent. The first of the six patients who died after emergency operation was an 87-year-old woman, classified ASA IVE, CRI III, who had been treated for 10 months with oral steroids (preoperative dose 20 mg day^{-1} hydrocortisone) for a Waldenström's macroglobulinaemia. She was operated on for small bowel infarction and her death on the 36th day after surgery from heart failure was not considered to be related to steroid. The second and the third patients were, respectively, men aged 65 and 71 years, both classified ASA IIIE, CRI III, who had been treated for 7 months with oral steroids (mean preoperative dose 100 mg day^{-1}) for chronic lymphocytic leukaemia with severe thrombocytopenia. They were operated on for acute cholecystitis, with choledocholithiasis in one case and ischaemic colitis in the other The latter patient died from septic shock Peroperative haemostasis was particularly difficult owing to tissue friability, especially of the liver, in the patient with choledocholithiasis. This patient died on the first day after operation from intraperitoneal bleeding This death was considered to be related to steroid The fourth and fifth patients who died were, respectively, men aged 60 and 66 years who were admitted to the intensive care unit for carbon dioxide narcosis. Both were classified ASA IVE, CRI IV They had been treated for 24 months with oral steroids (mean preoperative dose 60 mg day^{-1}) for severe chronic obstructive airways disease (COAD). They had subtotal gastrectomy to control massive haemorrhage from a bleeding duodenal ulcer and bleeding gastritis. They developed incisional hernia and were unable to be weaned from mechanical ventilation. As ventral hernia complicated the pulmonary problem, their deaths were considered to be steroid related. The sixth patient was a 68-year-old man who had ischaemic colitis after a cardiac arrest following carotid endarterectomy This death was not considered to be steroid related

Non-lethal postoperative complications were encountered in 13 patients Nine were related to preoperative steroid treatment (*Table 2*) The only secondary adrenal insufficiency encountered after operation was in a 58-year-old man with COAD who had been treated with hydrocortisone (20 mg day^{-1}) for 34 years and operated on as an emergency for acute faecal peritonitis from perforated diverticulitis. Peritoneal lavage and Hartmann's procedure were performed under general anaesthesia with 65 mg supplementary intravenous methylprednisolone. The parenteral steroid dose was reduced gradually during the first week after surgery and was replaced by 20 mg day^{-1} oral prednisolone on day nine. Subsequently, the patient insidiously developed lethargy, weakness, orthostatic hypotension and a mild hyperkalaemia up to 5·3 mmol/l. A short tetracosactrin stimulation test using 250 μg Synacthen® (Ciba Laboratories, Horsham, UK) showed no response of plasma cortisol and confirmed adrenocortical insufficiency which was reversed by supplementary oral steroid.

Four of the 13 non-lethal complications were not considered to be related to preoperative steroid impregnation: lymphatic fluid collection in the axilla after radical modified mastectomy (one case), deep femoral thrombosis 15 days after inguinal herniorraphy (two cases), and paralytic ileus following exploratory laparotomy in a patient with cerebral metastatic tumour.

No correlation could be found between the rate of steroid-related complications and the presence of clinical features of long-term steroid administration. In view of the high incidence of postoperative steroid-related morbidity in patients with bronchopulmonary disorders, a comparative study of two subpopulations was performed: group P (pulmonary disease as indication for steroid therapy, $n=27$) and group NP (non-pulmonary disorder, $n=28$). *Table 3* shows that while steroid dose was significantly lower in group P, duration of therapy was longer. Meaningful comparison of morbidity rates between group P and group NP was possible as the groups were comparable for age, sex, preoperative risk scores (ASA, CRI), type of surgery (intraperitoneal or extraperitoneal procedures) and number of emergency procedures The

Table 2 *Clinical data of nine patients who developed non-lethal steroid-related complications*

			Steroid therapy before operation					
Age (years)	Sex	Disease	Duration (months)	Hydrocortisone dose (mg day^{-1})	ASA*	CRI†	Type of operation	Steroid-related morbidity after operation
60	M	COAD	24	40	IVE	III	Suture of duodenal ulcer + omentoplasty	Recurrent pneumothorax
58	M	COAD	408	20	IIIE	II	Hartmann's procedure for perforated diverticulitis	Adrenal insufficiency
68	M	COAD	12	50	III	I	Right colectomy for adenocarcinoma	Evisceration
33	F	Atopic asthma	24	60	IIE	I	Bassini's procedure for strangulated inguinal hernia	Relapse of inguinal hernia with crural strangulated hernia
57	F	COAD	60	40	IIIE	I	Repair of umbilical hernia	Severe bronchospasm after extubation
65	F	COAD	18	100	IV	III	Puestow's procedure	Acute respiratory distress syndrome
71	M	COAD	61	30	IIIE	II	Repair of iatrogenic colonic perforation	Wound abscess and subsequent incisional hernia
86	M	COAD	12	48	IVE	IV	Hartmann's procedure for perforated diverticulitis	Wound sepsis and incisional hernia
30	F	Crohn's disease	2	150	III	II	Right colectomy	Wound sepsis

* American Society of Anesthesiologists' physical status[4], † cardiac risk index of Goldman *et al.*[5]; COAD, chronic obstructive airways disease

morbidity rate was significantly greater in group P than in group NP.

Table 3 *Comparison of surgical patients with pulmonary (P) or non-pulmonary (NP) underlying diseases*

	P ($n=27$)	NP ($n=28$)	*P*
Median (range) steroid dose* (mg day^{-1})	20 (15–100)	80 (20–480)	<0·01
Median (range) steroid dose (mg kg^{-1} day^{-1})	0·51 (0·20–2·56)	1·20 (0·23–7·38)	<0·01
Median (range) duration of steroid therapy (months)	24 (1–408)	6 (1–240)	<0·01
ASA† (>III/≤III)	17/10	14/14	n.s.
CRI‡ (>II/≤II)	14/13	12/16	n.s.
Emergency/elective surgery	11/16	13/15	n.s.
Steroid-related postoperative complications	10 (37%)	2 (7%)	0·016
Non-lethal steroid-related postoperative complications	8 (33%)	1 (4%)	0·037

* Steroid doses are expressed in mg day^{-1} hydrocortisone or equivalent; † American Society of Anesthesiologists' physical status[4]; ‡ cardiac risk index, Goldman *et al* [5]; n.s., not significant

The parameters of preoperative steroid therapy for each individual patient were plotted on the dose–duration graph (*Figure 1*). Eleven (34 per cent) of the 32 patients located above the derived equivalence curve developed steroid-related complications after operation, from which some died, compared with only one of the 23 patients located below the curve ($P=0{\cdot}014$). Nine out of sixteen patients from group P who were located above the curve developed steroid-related complications compared with two out of 16 patients from group NP who were similarly located above the curve ($P=0{\cdot}023$). This rate of 56 per cent for postoperative complications in patients on steroids for severe bronchopulmonary disorders was markedly higher than the rate of 12 per cent experienced in 520 general surgical patients with COAD who did not require steroid treatment. Furthermore, of the 23 patients located below the curve, 11 were in group P and only one (9 per cent) developed a steroid-related complication. The total rate of postoperative dehiscence or incisional hernia occurrence after intraperitoneal surgery was 13 per cent (five out of 40 patients), and the rate of recurrence after hernia repair was 9 per cent (one out of 11 patients). During the study period the rate of incisional hernia occurrence after abdominal surgery in 1580 patients, and of recurrence after hernia repair in 380 patients, was 2 per cent in those not treated with steroid.

Discussion

Assessment of operative risk classically includes the ASA[4] or CRI[5] scores. This particular population of chronically steroid-treated patients presented increased operative risk due to age, high ASA (>III in 56 per cent) and CRI (>II in 47 per cent) scores, high rate of emergency surgery, and severity of the steroid-treated underlying disease. Therefore, operative morbidity and mortality rates were expected to be high[5–11]. However, the specific adverse effects of preoperative steroid therapy are hard to discriminate from the other associated risk factors[12,13]. Steroid therapy is not even taken into account in determining the ASA, CRI or APS[4–6]. Nevertheless, steroid treatment was considered recently to constitute a risk factor independent of the acute physiology and chronic health evaluation (APACHE II) for abdominal sepsis and related mortality[7]. However, the nature of the underlying disease and the amount of steroid impregnation were not considered in this work, since neither duration nor dose was analysed[7]. In the present series, patients with bronchopulmonary disorders had a significantly higher rate of postoperative steroid-related complications, and this correlated with long duration with low-dose preoperative steroid. This indicates the particular relevance of duration of therapy when assessing steroid-related operative risk.

Adrenocortical function, measured by repeated plasma corticosteroid estimation, was studied by Kehlet and Binder[9] in chronically steroid-treated patients undergoing major surgical procedures without supplementary hormone administration. In that study all patients who received 12·5 mg prednisone or more for over 6 months, 10 mg or more for over 2 years, or 7·5 mg or more for over 5 years showed an impaired adrenocortical response to surgery. These doses are essentially physiological replacement regimens[14]. Repeating such a study further to assess adrenocortical function and clinical course would have been unethical and so the proposed equivalence equation was calculated[10] using the cutting points from the histogram provided by Kehlet and Binder. The equation, which is that of a hyperbolic curve, allowed an easy classification of patients according to their level of steroid impregnation (above or below the physiological dose) Data of patients located above or below the curve correspond respectively to high or low steroid impregnation. Therefore, as this model reflects, the level of steroid impregnation, albeit imperfectly, may allow further discrimination between high and low steroid-related postoperative complication risk This is strongly suggested by the data presented in this paper. Such a mathematical approach seems as justified as the simple compilation of signs or symptoms of exogenous hyperadrenocorticism, inasmuch as some patients receiving therapeutic doses of steroids develop Cushingoid changes whereas others receiving comparable doses do not. For instance the tendency of a given dose to cause Cushingoid changes is exaggerated if hypothyroidism or liver disease is present.

Although these results need further assessment in larger, prospective series, it appears that steroid prescribed for pulmonary disorders constitutes a potentially higher risk of complication than steroid prescribed for non-pulmonary disorders. For example, a patient with COAD receiving 15 mg methylprednisolone for more than 1 year presents a higher risk of complication than a patient with idiopathic thrombocytopenic purpura receiving 60 mg methylprednisolone for 2 months. Both patients have received steroid doses large enough to produce part or all of the syndrome of exogenous hyperadrenocorticism. Whether the complication is directly or indirectly related to steroid therapy is difficult to ascertain. For instance, dehiscence may be due to aggressive physical and respiratory therapy while postoperative pneumonia may be due to pusillanimous respiratory therapy through fear of causing incisional hernia. Nevertheless the complication rate of 56 per cent in COAD patients receiving steroid was dramatically higher than that of 12 per cent in general surgical COAD patients who did not take steroid. This reflects the contribution of steroid therapy to morbidity in patients with pulmonary disease.

In conclusion, this study reviewed 55 chronically steroid-treated patients undergoing surgical procedures. The probability of developing steroid-related complications after operation was higher in patients with COAD for which they required steroid therapy. The duration of steroid therapy in this subpopulation was longer than that in patients without pulmonary disease. The amount of steroid impregnation and the nature of the underlying disease for which steroid is administered should be considered together when assessing the risk of steroid-related complications.

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Premorphological metabolic changes in human breast carcinogenesis

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Malignant breast tissue is characterized by morphological and metabolic changes when compared with normal breast tissue. In this study, the cytochemical measurement of glucose-6-phosphate dehydrogenase (G6PD) activity was used to detect abnormal metabolism in breast tissue and to determine whether abnormal metabolic activity precedes morphological change during human breast carcinogenesis. Normal and benign breast tissue, morphologically normal tissue from cancer-containing breasts, and malignant breast tissue were studied. In malignant tissue, mean(s.e.m.) G6PD activity was significantly increased when compared with normal and benign tissue (9·69(2·3) versus *27·02(1·7) mean integrated extinction (MIE) × 100,* $P<0.01$*). G6PD activity was increased in morphologically normal tissue from cancer-containing breasts when compared with normal and benign breast tissue from breasts with no known cancer (27·02(1·7)* versus *18·42(2·6) MIE × 100,* $P<0.05$*). These findings suggest that metabolic abnormalities precede morphological changes in breast carcinogenesis. Abnormal metabolism can be detected widely within a cancer-containing breast. The detection of such abnormality may prove helpful in identifying patients at high risk of developing breast cancer.*

Keywords: Breast neoplasms, glucose phosphate dehydrogenase, histocytochemistry, oxidoreductases, carcinogenesis

In breasts removed at the time of mastectomy for breast cancer, a morphological continuum from normal epithelium to invasive breast cancer can be seen: hyperplasia, atypical hyperplasia and carcinoma *in situ*[1]. There is variation in the metabolism of normal and malignant breast tissues and this may be detected by differences in enzyme patterns between these tissues[2].

The aim of the present study was to determine whether metabolic abnormality can be detected in breast tissue at high risk of developing cancer before morphological change is seen.

Glucose-6-phosphate dehydrogenase (D-glucose-6-phosphate: $NADP^+$ 1-oxidoreductase; G6PD; EC 1.1.1.49) is a key rate-limiting enzyme in the pentose phosphate pathway. This pathway is important in cellular metabolism because it is the major source of pentose sugars and reduced nicotinamide adenine dinucleotide phosphate (NADPH). The pentose sugars are essential for nucleic acid synthesis. NADPH is necessary not only for fatty acid and steroids biosynthesis but it also provides reducing power within the cell.

Laboratory and clinical evidence suggests that G6PD has an important role in carcinogenesis. Weber has proposed that increased G6PD activity is a transformation-linked event in carcinogenesis[2]. Quantitative differences in G6PD activity have been shown between normal and malignant tissue in the rat 7,12-dimethylbenz(a)anthracene-induced model of mammary carcinogenesis[3]. Similar findings have been reported in human breast, gastric and colonic tissues[4,5]. Epidemiological studies provide evidence that hereditary G6PD deficiency protects against the development of cancer[6,7]. Experimental evidence to support this hypothesis has been provided by Feo *et al.* who found that fibroblasts from humans with G6PD deficiency were resistant to benzo(a)pyrene-induced *in vitro* transformation[8]. This effect could be mimicked in normal fibroblasts by the addition of dehydroepiandrosterone, which is a strong inhibitor of G6PD[9].

In view of the importance of G6PD in normal cellular metabolism and in carcinogenesis this enzyme was selected for study as a marker of metabolic activity.

Patients and methods

Patients and tissues

The following tissues were harvested: (1) normal and benign breast tissues were taken from breasts with no known breast cancer (normal breast tissue). This tissue was collected at the time of excision biopsy of breast lumps. Normal breast tissue was collected from the tissue surrounding a fibroadenoma; (2) morphologically normal breast tissue was removed from the quadrant diametrically opposite the index cancer at the time of mastectomy for breast cancer (remote breast tissue). The tissue analysed was at least 5 cm from the macroscopic edge of the cancer; and (3) malignant breast tissue was excised at the time of mastectomy or excision biopsy.

The tissue was rejected if no epithelial tissue was present when stained with methylene blue at the time of sectioning or if epithelial hyperplasia, apocrine metaplasia or cyst formation was found on haematoxylin and eosin staining. The number of tissues initially examined and those found to be suitable for complete analysis are shown in *Table 1*. The median age and age range of the patients in each group are shown in *Table 2*.

Methods

The technique used for the cytochemical measurement of G6PD activity in this study was described by Altman[10] and reviewed by van Noorden who found it to be precise, reproducible, specific and valid[11]. The method consists of four parts.

Collecting and chilling the tissue. The specimen was harvested within 10 min of excision and placed in Trowell's T8 medium (GIBCO, Paisley, UK). Representative tissue samples were taken and the samples were divided into 5 mm^3 pieces. This tissue was then supercooled in −70°C *n*-hexane (BDH Chemicals, Poole, UK) for 30–60 s. The tissue was stored at −70°C Analysis was performed within 1 week of harvesting.

Sectioning the tissue. The supercooled tissue blocks were mounted on chucks and sectioned at 10 μm on a Slee TE cryostat (Slee Medical Equipment Ltd., London, UK). The cabinet temperature was maintained at −30°C and the knife was cooled to −70°C. Preliminary sections from each block were stained with methylene blue to ensure the presence of epithelial cells. Parallel sections were taken for haematoxylin and eosin staining Sections to be reacted for G6PD

Table 1 *Total number of tissues collected and fully analysed*

Tissue type	No. collected	No. adequate for study
Normal	43	31 (72)
Remote	50	26 (52)
Malignant	64	58 (91)
Total	157	115 (73)

Values in parentheses are percentages

Table 2 *Age and age range of patients*

Tissue type	No of specimens	Median age in years
Normal	31	34 (19–64)
Remote	26	45 (26–78)
Malignant	58	59 (28–84)
Total	115	50 (19–84)

Ranges are given in parentheses

activity were mounted three to a slide and stored in the cryostat cabinet In all cases duplicate sections were reacted.

Reacting the tissue. The slides were removed from the cryostat and the sections were surrounded by a Perspex ring (ICI Ireland Ltd., Dublin, Ireland), the lower rim of which was smeared with petroleum jelly to maintain a watertight seal with the slide The slides were left at room temperature for 5 min and then transferred into the reaction chamber at 37°C for another 5 min. The final composition of the reaction medium was 0·05 M glycylglycine in sodium hydroxide buffer with 30 per cent weight/volume polyvinyl alcohol to a final pH of 8·0, 5 mM neotetrazolium hydrochloride; 5 mM glucose-6-phosphate, 3 mM $NADP^+$; and 0·65 mM phenazine methosulphate. A schematic representation of the reaction is shown in *Figure 1*. The reaction medium was saturated with 100 per cent nitrogen at 37°C by bubbling gas through the medium for 2 min. The medium was then decanted into the Perspex ring. Both sets of slides were reacted in an atmosphere of nitrogen for 10 min At the end of the reaction period, the medium was washed off the slide with distilled water at 37°C.

Quantitating the reaction. The slides were mounted in Farrant's medium (Raymond Lamb, London, UK) for 60 min before being read The slides were read with a Vickers M85 scanning and integrating microdensitometer (Vickers Instruments Ltd., York, UK) at 585 nm, the isobestic point for the formazans of neotetrazolium hydrochloride. The scanning spot was set at 0·22 μm and × 100 objective was used The mask size was chosen by the best fit around the individual cells in the section In each of the duplicate sections at least 25 individual cells were read and the mean value was taken. Thus a total of 50 cells was analysed for each tissue Machine units were converted to mean integrated extinction (MIE) by reference to a standard filter For convenience, the value was then multiplied by 100 to avoid the continual use of the decimal point[12] The average value of the duplicate slides was taken.

All the slides were read in a blind fashion by a single observer. The cells selected were chosen at random when scanning the slide in a raster pattern

Statistical analysis

The results are shown as means and 95 per cent confidence intervals After the data were checked for homogeneity of variances, a one-way analysis of variance (ANOVA) with Tukey–Kramer procedure was used to look for differences between the groups[13] Linear regression analysis was used to look for correlation with continuous data and Spearman rank correlation was used with ordinal data

Results

Variation within the test

Within each slide the mean coefficient of variation of G6PD activity was 4·5 per cent. Between duplicate slides the mean difference was 9·6 per cent. In five samples of each tissue type, multiple blocks were analysed The mean intrablock and interblock coefficients of variation were 11 and 15 per cent, respectively.

G6PD activity and patient and tumour characteristics

G6PD activity and age. Within each patient group there was no correlation between the age of the patient and G6PD activity (normal breast tissue, correlation coefficient = 0·13, d f. = 30, $P = 0{\cdot}47$; remote breast tissue, correlation coefficient = −0·23, d.f. = 25, $P = 0{\cdot}25$; malignant breast tissue, correlation coefficient = −0·12, d.f. = 57, $P = 0{\cdot}37$).

G6PD activity and oestrogen receptor status When linear regression analysis was performed between G6PD activity and tumour oestrogen receptor status no correlation was found (correlation coefficient = 0·05, d.f. = 49, $P = 0{\cdot}73$).

G6PD activity and tumour differentiation. The tumour differentiation was measured according to a modified Bloom and Richardson method with scores given to host lymph node response, tumour necrosis, tubule formation, nuclear pleomorphism and mitotic rate[14]. The individual scores were added to give an overall grading There was no correlation between G6PD activity and the histological grade of the tumour (Spearman rank correlation = 0·13, $P = 0{\cdot}16$).

Comparison of G6PD activity in different tissue types

In *Table 3* the results of ANOVA together with Cochran's C test for homogeneity of variances can be seen. The G6PD activity at 10 min in the three tissue types in an atmosphere of nitrogen expressed as MIE × 100 is shown in *Figure 2*. There are significant differences between all three groups using the Tukey–Kramer procedure[13]. There is higher activity in malignant tissue when compared with normal or remote tissue. In remote tissue, the activity is significantly greater than in normal tissue ($P < 0{\cdot}05$).

Discussion

This study demonstrates that in morphologically normal tissue within a cancer-containing breast there is abnormal metabolic

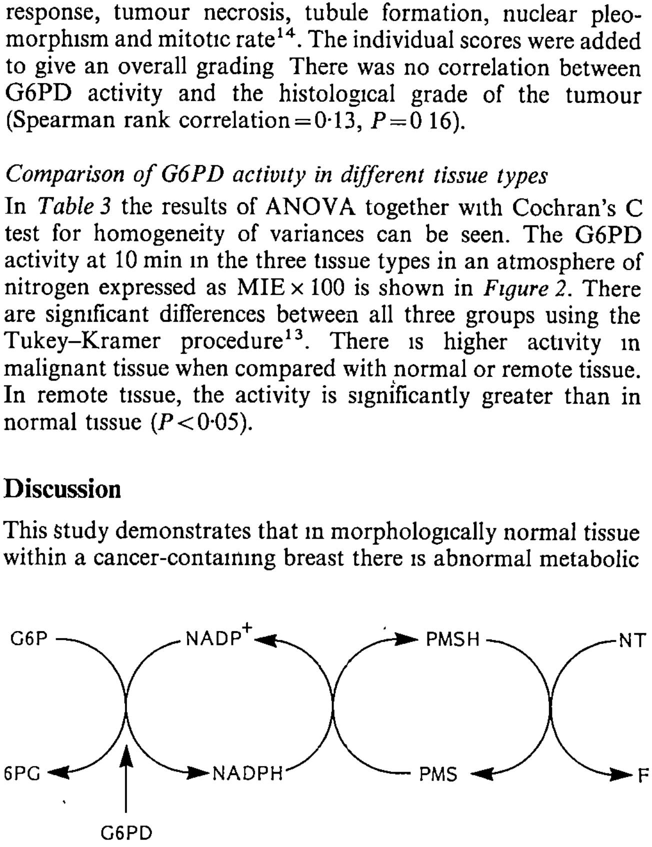

Figure 1 *Reaction sequence for measurement of glucose-6-phosophate dehydrogenase (G6PD). G6PD catalyses the conversion of glucose-6-phosphate (G6P) to 6-phosphogluconolactone (6PG) A chain of oxidation/reduction reactions results in the reduction of soluble colourless neotetrazolium (NT) to insoluble coloured formazan (F) which is precipitated at the site of reaction. Phenazine methosulphate (PMS) acts as an intermediate hydrogen acceptor, converting to reduced PMS (PMSH). The reaction occurs rapidly and quantitatively in an atmosphere of nitrogen $NADP^+$, nicotinamide adenine dinucleotide phosphate, NADPH, reduced form of $NADP^+$*

Table 3 *Analysis of variance*

Source of variation	Sum of square	d.f	Mean square	F-ratio	*P*
Between groups	6202·81	2	3101·40	18·19	<0·001
Within groups	19098·53	112	170·52		
Total (corrected)	25301·34	114			

Cochran's C test 0·347; $P = 1$. d f., degrees of freedom

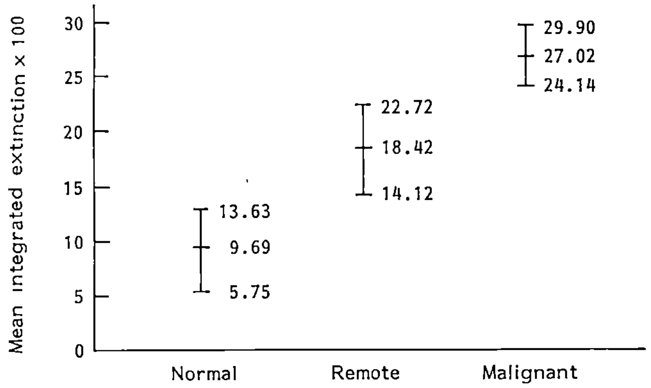

Figure 2 *Glucose-6-phosphate dehydrogenase activity in nitrogen at 10 min with Tukey–Kramer 95 per cent confidence intervals*

activity This abnormal metabolic activity occurs widely within the cancer-containing breast.

The groups were not age matched, however, because patients developing breast cancer are generally older than patients with benign breast disease. The chance of finding normal epithelial tissue in the mastectomy specimens from younger patients was higher than in older patients (*Table 1*). Normal epithelium could be found in only 52 per cent of mastectomy specimens. This resulted in the median age of the remote group being less than that of the malignant group (*Table 2*) This age difference in the three groups is unlikely to account for the findings The age difference would tend to bias the results towards finding higher levels of G6PD activity in younger patients for the following reasons In the present study there was no correlation between age and G6PD activity Previous studies of G6PD activity in normal breast tissue have shown that it decreases with age[15]. G6PD activity is higher in rapidly dividing tissue[16]. Breast tissue turns over more rapidly in young women as evidenced by a higher thymidine labelling index[17]. G6PD is induced by oestrogen[18]. Oestrogen levels are higher in younger than in older women[19].

It is unlikely that these abnormalities are due to paracrine effects. The remote tissue was taken in the diametrically opposite quadrant to the index cancer and at least 5 cm away from it.

There was no correlation between the tumour oestrogen status and G6PD activity. This is in keeping with two other studies[20,21]. Other studies found a significant correlation; three showed a positive correlation and one had a negative correlation[22–25]. There was no correlation between histological grade and G6PD activity. This confirms the findings of Poulsen and Frederiksen[21]

Jensen *et al.* found that normal lobules from a cancer-containing breast induced angiogenesis (a feature of malignant tissue) in a significantly greater percentage of cases than lobules from a breast with no known cancer[26]. Mansel *et al.* found that an antigen detected by monoclonal antibody 323A3 was found in 73 per cent of normal lobules from a cancer-containing breast but not in normal lobules from breasts without a cancer. This antigen can be detected in 65 per cent of breast cancers[27] Spring-Millis and Elias, using scanning electron microscopy, reported structural abnormalities in lobules from cancer-containing breasts which clearly distinguished them from lobules from non-cancer-containing breasts[28].

These widespread changes in normal lobules from cancer-containing breasts are consistent with the high incidence of multifocality and bilaterality in breast cancer[29,30] This clinical finding and these laboratory findings suggest that malignant transformation is widespread in a cancer-containing breast

It has been shown in other models of carcinogenesis that abnormalities of G6PD activity can be detected before morphological change. Hayden found that abnormalities of G6PD activity precede the development of squamous cell carcinoma in the dimethylbenz(a)anthracene-induced model of palatal carcinoma in the rat[31]. Bannasch *et al.* noticed the same finding in the N-nitrosormorpholine-induced hepatocarcinoma in the rat[32]. Yashishita noted similar findings in rat bladder cancer induced by N-butyl-N-butanol(4)nitrosamine and concluded. 'G6PD plays an important role in the elucidation of carcinogenic process and will be a good marker for the early diagnosis of a tumour'[33] In human tissue, Pearse and Marks studied the G6PD activity in normal human buttock skin (unexposed to sunlight), solar keratosis (premalignant lesion), paralesional chronically exposed skin and buttock skin irradiated with ultraviolet light[34]. There was an increase in G6PD activity in all areas when compared with normal buttock skin. Vatn *et al.* found raised G6PD activity in premalignant colonic mucosa[35].

The activation of tyrosine kinase from the cytoplasmic domain of epidermal growth factor receptor, in response to the binding of the receptor, results in the phosphorylation of G6PD[36] The presence of epidermal growth factor receptors is associated with a poor prognosis in patients with breast cancer[37]

The alteration in G6PD activity may be due to generalized changes in the hormonal milieu of the patient Dehydroepiandrosterone suppresses G6PD activity. Conversely, oestrogen tends to increase G6PD activity There is evidence that the excretion of dehydroepiandrosterone is decreased in patients with breast cancer and in women with a high risk of developing breast cancer[38] Raised oestrogen activity is associated both experimentally and clinically with an increased incidence of breast cancer. The elevated G6PD activity found in the present study may be the result of these hormonal influences.

This study demonstrates a metabolic continuum in breast carcinoma similar to the morphological continuum and suggests that metabolic changes precede morphological changes. The widespread distribution of this abnormality is in keeping with the high incidence of multifocality in breast carcinoma[29]

The possibility of measuring G6PD activity on needle aspirates of breast tissue is being explored with the aim of detecting such high-risk epithelium. It is feasible to obtain sufficient epithelial cells for the immunohistochemical measurement of oestrogen receptor content from normal breasts by fine-needle aspiration[39] A significant increase in G6PD activity in the absence of cytological abnormality may be an indication for close surveillance.

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Short note

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Selection of patients with internal intussusception of the rectum for posterior rectopexy

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Dynamic defaecography plays a key role in the diagnosis of internal rectal intussusception, although the pathophysiological mechanism, clinical picture and correct treatment are far from clear. This prospective study was designed to analyse the correlation between symptoms and defaecographic findings by evaluating the effect of posterior rectopexy on these symptoms and findings.

Patients and methods

Between January 1985 and October 1988, 11 women and two men, aged 30–77 years (mean 57 years), underwent posterior rectopexy by the Wells technique for internal intussusception[1,2]. A variety of symptoms, such as incomplete evacuation after defaecation, faecal incontinence, constipation, unsuccessful urge to defaecate and pain in the perianal region, occurred in this group, as determined by a questionnaire filled out before and at 3 and 6 months after operation. Dynamic defaecography was performed on all patients. To visualize the rectum during defaecography, 120 ml high density $BaSO_4$ suspension, and 120 ml $BaSO_4$ Metamucil® suspension (Searle, Maarssen, The Netherlands) to increase bolus viscosity was introduced. If there was no urge to defaecate, the volume was increased up to 500 ml. Films and video recordings were taken at rest, during straining, restraining and during defaecation. If the distance between the vagina and rectum exceeded 5 mm during defaecation, the dynamic defaecogram was repeated after drinking two glasses of $BaSO_4$ suspension to detect an enterocele. Fisher's exact test was used for statistical evaluation[3].

Results

In four patients, the distance between the vagina and rectum increased during defaecation. These patients appeared to have an enterocele, three with small bowel loops and one with sigmoid loops (*Figures 1a* and *b*). The sensation of incomplete evacuation after defaecation disappeared in all four patients after operation. In the remaining nine patients, the sensation of incomplete evacuation was beneficially influenced in only two. The effect on this specific symptom was significantly better in those with an enterocele ($P < 0{\cdot}05$).

Faecal continence was regained after surgery in all four incontinent patients, two of whom had an enterocele. Constipation was cured in only two of six patients; unsuccessful urge to defaecate and low pelvic pain improved in six of eight patients. These results did not depend on the presence or absence of a coexisting enterocele. Five of the 13 patients had internal intussusception without a preceding anterior rectocele during defaecation (*Figures 2a* and *b*). The distance between the anterior aspect of the sacrum and the rectum at rest was 20 mm in one patient, 16 mm in one patient and less than 16 mm in three patients. The normal range is 5–16 mm[4]. In the remaining eight patients, an anterior rectocele preceded internal intussusception during defaecation and the rectosacral distance was within the normal range. No symptom could specifically be related to the presence or absence of an anterior rectocele. Postoperative dynamic defaecography was normal in all 13 patients.

Discussion

Posterior rectopexy for complete rectal prolapse is performed worldwide on a large scale with excellent results. However, the effect of this operation on symptoms ascribed to internal intussusception is unpredictable and posterior rectopexy for this syndrome is increasingly criticized. Having observed a successful outcome in some patients, we have tried, on a prospective basis, to define justifiable criteria for the operation.

The sensation of incomplete evacuation is a symptom often ascribed to internal intussusception. The activity of the stress

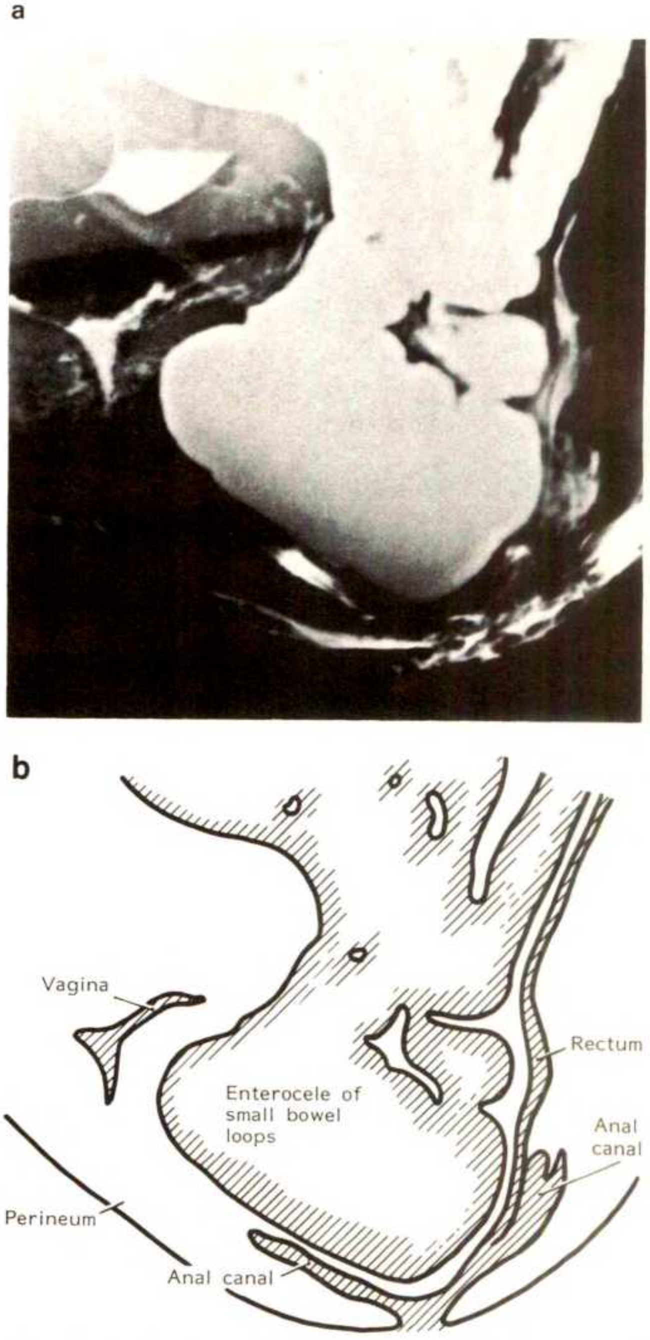

Figure 1 **a** *Radiograph during defaecation after oral contrast administration. An enterocele is responsible for the increased distance between vagina and rectum;* **b** *schematic representation of* **a**

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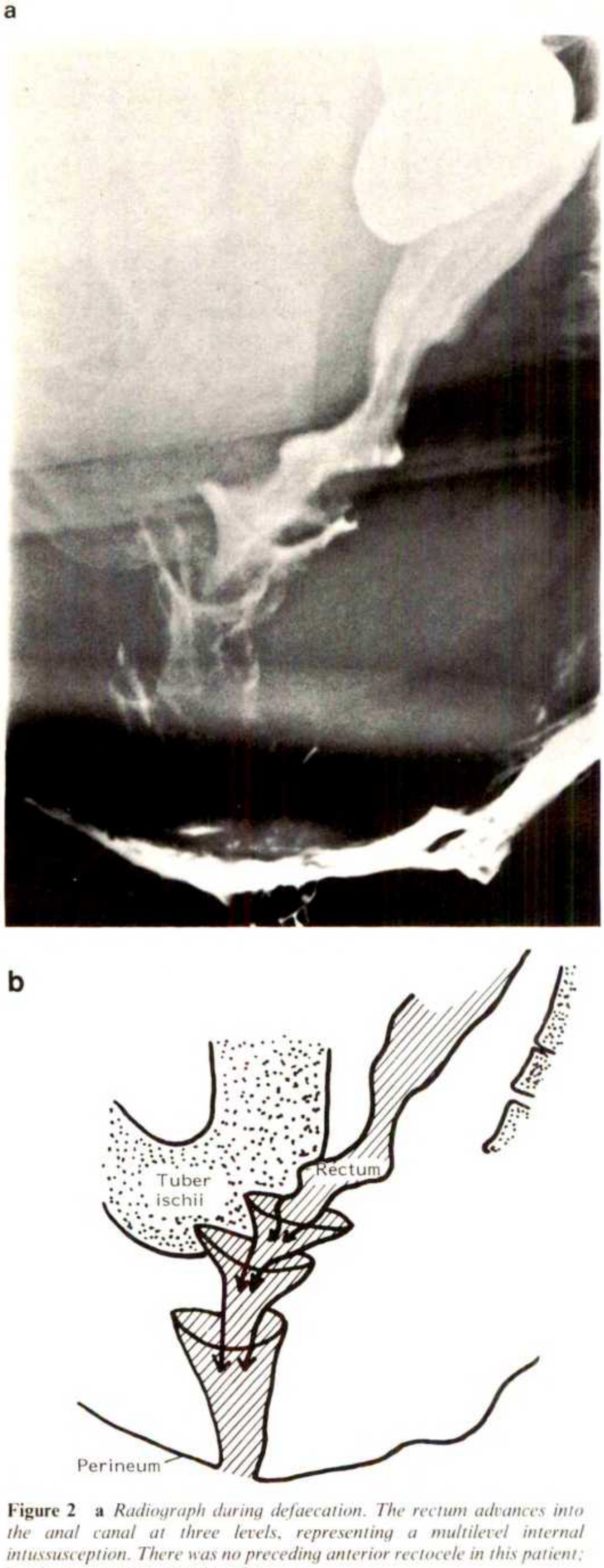

Figure 2 **a** *Radiograph during defaecation. The rectum advances into the anal canal at three levels, representing a multilevel internal intussusception. There was no preceding anterior rectocele in this patient;* **b** *schematic representation of* **a**

receptors in the anal canal, distended by the intussuscepted rectum, is believed to be the origin of the sensation of incomplete evacuation after defaecation[5–9]. In cases of internal intussusception without a coexisting enterocele this symptom improved in only two of nine patients after operation, so the suggested relationship between distal rectal distension and sensation of incomplete evacuation was not confirmed in this study. We believe that an enterocele is a major factor in provoking the sensation of incomplete evacuation since all four patients with enterocele were relieved of this sensation by surgery. The effect of operation on the coexisting complaints of constipation, pain, etc. was equally poor in those with and without an enterocele. In healthy asymptomatic people an enterocele is not found on defaecography, whereas internal intussusception has been shown to be relatively common in such people[10].

An anterior rectocele is considered to be a precursor of an internal intussusception. The surplus rectal mucosa may be forced into the anal canal during relaxation of the sphincter complex and this is best demonstrated by dynamic defaecography[5,8,9,11–14]. Before the event of internal intussusception, an anterior rectocele was evident in eight patients. In the remaining five, no anterior rectocele was present during straining or defaecation. This subdivision turned out to be of no clinical relevance, since the presence or absence of an anterior rectocele was not related to any of the presenting symptoms.

An increase in distance between the rectum and the anterior aspect of the sacrum has also been proposed as a possible cause of internal intussusception[5,6,11,15]. Only one of our patients showed a clear increase in this distance, one was borderline and the other three were within the normal range, and so this theory cannot be substantiated by the present study.

Patients with a sensation of incomplete evacuation as a predominant symptom, with internal intussusception in combination with an enterocele, should be considered candidates for posterior rectopexy.

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Short note

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Colostomy irrigation: a clinical and scintigraphic comparison between three different irrigation volumes

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The majority of colostomy patients prefer irrigation to natural stomal evacuation[1,2] and many obtain stomal continence[3] Irrigation, however, is time consuming and not without discomfort and inconvenience[4,5]. The volumes of water used range from 250 to 1200 ml[1,6] and 1000 ml is a typical recommendation[2–5]. The present randomized study compares the effects of irrigation volumes of 250, 500 and 1000 ml.

Patients and methods

Twelve out-patients were randomized and 11 completed the study. There were seven men and four women of median age 54 years (range 38–78 years). All had a left lower quadrant sigmoid colostomy, eight for the treatment of rectal cancer, two for diverticular disease and one for anorectal malformation. All patients were well adjusted to irrigation which they had used for between 6 months and 7 years The irrigation volume used was 1000 ml in eight patients and 2000, 750 and 400 ml respectively in the other three Eight patients irrigated daily and three every second day

The study had a cross-over design in which each patient assessed the daily irrigation volumes 250, 500 and 1000 ml in random sequence in three consecutive 2-week periods. The patients recorded duration of fluid inflow and colonic emptying, faecal consistency, abdominal pain after irrigation, and any faecal incontinence between irrigations

A double isotope technique was developed to evaluate colonic emptying of irrigation fluid and faecal content. The technique was used three times in each patient, always in the middle of the 2-week study periods Radioactive labelling of colonic contents was achieved by the ingestion of 10 MBq ^{51}Cr-EDTA 24 h before scintigraphic investigation Following a light morning meal the patient irrigated in front of a γ-camera (Siemens, Ballerūp, Denmark, ZLC 370 coupled to a scintiview system with data storage on floppy discs) with the allocated volume of tap water, at 37°C, which contained 200 MBq ^{99m}technetium pertechnetate. The evacuation of ^{51}Cr-labelled faecal content as well as inflow and outflow of ^{99m}Tc-labelled irrigation fluid was then followed with the γ-camera throughout the irrigation procedure. The ratio of ^{99m}Tc activity in the final scintigram compared with the initial scintigram allowed calculation of the volume of retained fluid. All assessments and most of the statistical analyses were carried out on a blind basis. The trial was in accordance with the Second Declaration of Helsinki and informed consent was obtained from each patient

We estimated that with the cross-over design a sample size of 12 was required to give 90 per cent power to detect differences between neighbouring volumes of 60–70 per cent of the between-patient standard deviation We used non-parametric methods where they were available (Friedman test, Page test for ordered alternatives, Cochran's *Q* test for binomial outcomes), and parametric methods for the more complex repeated measures analysis of variance

We found no evidence of systematic differences between days within the 2-week study periods, and accordingly calculations were based on sums or medians over these periods There was no evidence of any period- or carry-over effects

Table 1 *Median irrigation inflow and outflow times in 11 patients, calculated for each patient as the median of 14 irrigations*

Time (min)	Volume (ml) 250	500	1000
Inflow	2·3	3·0	6·4
Outflow	25·1	25·3	25·1

Results

There was a highly significant relationship between irrigation volume and duration of inflow ($P<0·001$) but there was no analogous relationship with regard to duration of outflow. In a two-way analysis of variance there was accordingly a significant interaction ($P<0·01$; *Table 1*). There was no relationship between volume of irrigation and pain or discomfort, but a volume of 1000 ml resulted in significantly less solid faecal consistency ($P<0·05$), while volumes of 250 ml and 500 ml did not differ in this respect. Faecal incontinence between irrigations was significantly more frequent after a volume of 250 ml than after the other volumes ($P<0·05$). Eight patients preferred an irrigation volume of 500 ml, two preferred 1000 ml and one preferred 250 ml ($P<0·025$)

Scintigraphic investigation showed no statistically significant differences in the localization of ^{51}Cr-EDTA (ethylenediamine-tetra-acetic acid) labelled colonic contents before irrigation. Typically the isotope accumulations were in the ascending colon In two patients using 250 ml and one patient using 1000 ml no ^{51}Cr-EDTA was detected. Following the introduction of ^{99m}Tc-pertechnetate-labelled irrigation fluid, the isotope was dispersed throughout the large intestine The median amount of retained fluid following 250, 500 and 1000 ml irrigations was 11, 25 and 28 ml respectively ($P<0·001$). Retained irrigation fluid was predominantly located in the caecal region. Complete emptying of ^{51}Cr-EDTA-labelled colonic contents was obtained in all patients.

Discussion

Most of the patients were in the habit of using an irrigation volume of 1000 ml. Given the opportunity to choose between 250, 500 and 1000 ml, a majority preferred 500 ml.

As expected the duration of irrigation fluid inflow was related to volume. Surprisingly, the washout time was almost independent of irrigation fluid volume, but time was determined by the patient's own record and might reflect habit rather than sensation of colonic emptying. Scintigraphic evaluation 8 min after the start of irrigation fluid outflow revealed only minor differences in fraction of expelled colonic content; for the irrigation volumes 250, 500 and 1000 ml respectively, 27, 35 and 26 per cent of the instilled volume was emptied. This might indicate an equal washout time irrespective of irrigation fluid volume. The statistically significant difference in retained irrigation fluid volume at the end of washout is probably clinically insignificant. Although ^{51}Cr-EDTA was ingested as a bolus the isotope had accumulated throughout the large intestine, including the ascending colon, 24 h later. Scintigraphic evidence of complete evacuation of this isotope was assumed to represent complete colonic emptying of faecal content following irrigation.

It appears that the general recommendation of a daily irrigation fluid volume of 1000 ml is not optimal for all patients. A reduced volume of 500 ml seems more appropriate because of patient preference, reduced inflow time, complete colonic emptying of more consistent faecal contents, and a small

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amount of retained irrigation fluid. A further reduction in irrigation volume resulted in increased faecal incontinence between irrigations. The double isotope scintigraphic technique allowing an objective assessment of colostomy irrigation might be useful in the education (video instruction) of patients with problems related to irrigation. Furthermore, it might be used for the evaluation of the effects of drugs or irrigation fluids intended to improve colonic emptying or to reduce washout time.

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Surgical workshop

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Treatment for paraphimosis: the 'puncture' technique

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Paraphimosis is a surgical emergency which requires prompt intervention. Most surgeons attempt manipulative reduction first. A number of techniques have been described to reduce the oedema distal to the constricting ring. These include manual compression which can be enhanced by bandaging with a strip of rubber tissue[1] or injecting hyaluronidase[2]. We describe a simple and effective technique which facilitates manipulative reduction of paraphimosis.

Technique

The patient is given analgesia as required. A series of puncture holes are made in the swollen foreskin distal to the constricting ring with a 21 G hypodermic needle (*Figure 1*). By gently compressing the foreskin the majority of the oedema fluid is rapidly expressed, resulting in effective diminution of the swelling and easy manual reduction of the prepuce. Circumcision can be subsequently considered as an elective procedure.

Discussion

Manual compression of the paraphimosis requires forceful dissipation of oedema fluid past the constricting ring. We believe that the technique of puncturing the oedematous foreskin to drain the fluid externally is simple and allows rapid reduction of the paraphimosis with minimal discomfort to the patient.

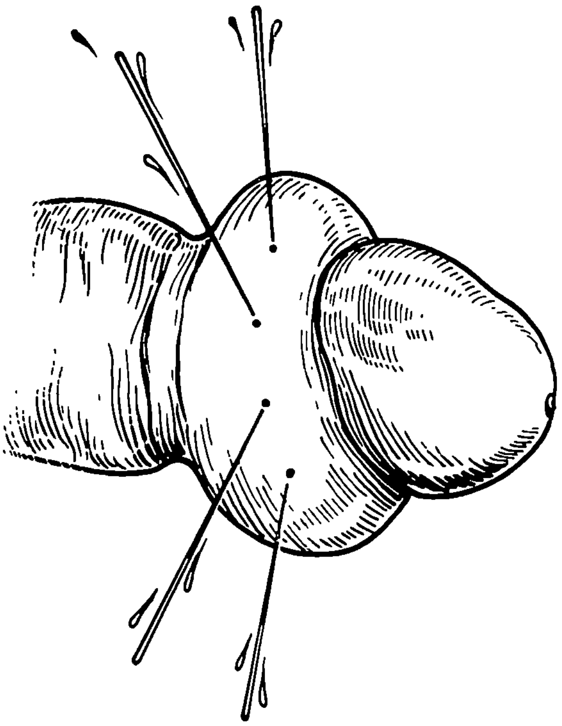

Figure 1 *Punctured oedematous foreskin with fluid draining externally*

Acknowledgements

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Treatment of trans-sphincteric fistulae by full thickness anorectal advancement flaps

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The 'laying open' technique has remained for many centuries the standard method of treating fistulae-*in-ano* with tracks below puborectalis. The success of this procedure depends on the incidence of intersphincteric (low anal) fistulae. 'Laying open' trans-sphincteric (high anal) fistulae involves division of the greater part of the external anal sphincter and may result in incontinence. Furthermore, in the presence of Crohn's disease, healing of the cavity may be impaired.

To overcome these problems we have treated patients with trans-sphincteric fistulae with an anorectal advancement flap technique.

Patients and methods

Eight patients, all of whom had previously been treated for recurrent anorectal sepsis, were referred with high trans-sphincteric fistulae during a 2-year period from 1987 to the present time They comprised four women and four men with an average age of 33 years (range 18–67 years)

Six patients had Crohn's disease, two with terminal ileitis and four with proctocolitis Each of these patients had presented between 3 and 8 years previously with an ischiorectal abscess which was treated by simple drainage Histology of tissue from the abscess wall confirmed Crohn's type granulomata No patients underwent excisional abdominal surgery prior to the anorectal advancement flap procedure However, all patients were clinically in remission and there was no macroscopic evidence of Crohn's proctitis

Two patients without evidence of associated disease had trans-sphincteric fistulae with horseshoe tracts and internal openings above the dentate line. They had both previously undergone a 'laying open' procedure but had developed recurrent fistulae-*in-ano*. One of these patients had noted a deterioration in continence for faeces after a 'laying open' procedure 4 years previously

All patients received mechanical bowel preparation, antibiotic prophylaxis and were treated under general anaesthesia in the lithotomy position using a standard technique. The tract(s) was identified with a probe and marked with a nylon loop. The internal opening was exposed using two Gelpi's retractors (Seward, Middlesex, UK) and excised with an elliptical incision, approximately half the circumference of the anorectal canal (*Figure 1*). A full thickness of rectal wall was dissected proximally using cutting diathermy to minimize bleeding (*Figure 2*) The mucosa distal to the internal opening was elevated for a short distance The internal opening of the fistulous track was closed with 2/0 Vicryl (Ethicon Ltd., Edinburgh, UK) sutures The mobilized rectal wall was then advanced over the closed end of the track and anastomosed to the anal canal with interrupted absorbable sutures.

The external component of the fistulous track was managed by drainage rather than excision. Skin around the external opening was excised and the granulation tissue lining the track curretted The resulting cavity was drained externally using a No 8 Foley catheter or Penrose drain for approximately 1 month after operation.

Results

There was no ischaemic necrosis of the rectal flap and primary healing of the anorectal anastomosis was achieved in six patients. The mean duration of hospital stay was 6 days (range 5–9 days). Complete healing of the perineum occurred in six patients. The average time to complete resolution of the external compartment of the fistula was 9 weeks, between the first (6 weeks) and second (3 months) out-patient visits No patient required home treatment by a general practitioner or district nurse.

In one patient with an idiopathic horseshoe track, the fistula recurred. The extrasphincteric cavity had been drained using a No. 8 Foley catheter which was accidentally removed on the fifth postoperative day. The fistula was therefore drained with a rubber seton and 3 months later the procedure was repeated with a further anorectal advancement flap. Eight weeks after operation the fistula had completely healed.

Early recurrence also occurred in one patient with Crohn's disease. Examination under anaesthesia revealed changes of Crohn's proctitis. This patient currently has a seton *in situ* and is receiving aggressive medical treatment. He will be considered for a further anorectal advancement flap procedure when complete remission is achieved.

Seven patients have normal continence at follow-up ranging from 2 months to 2 years. There has been no further

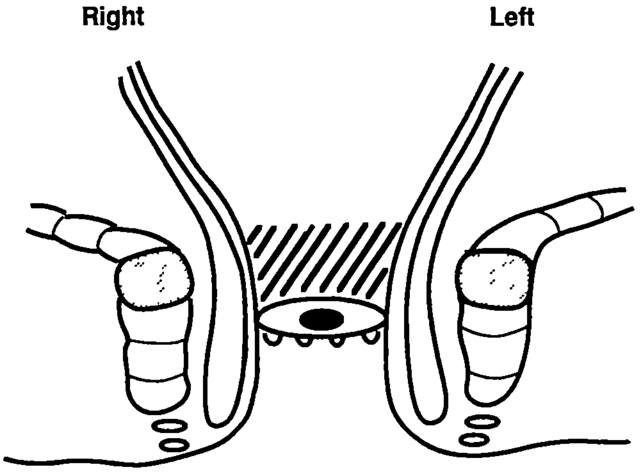

Figure 1 *Coronal section of the anorectal region showing excision of the internal opening*

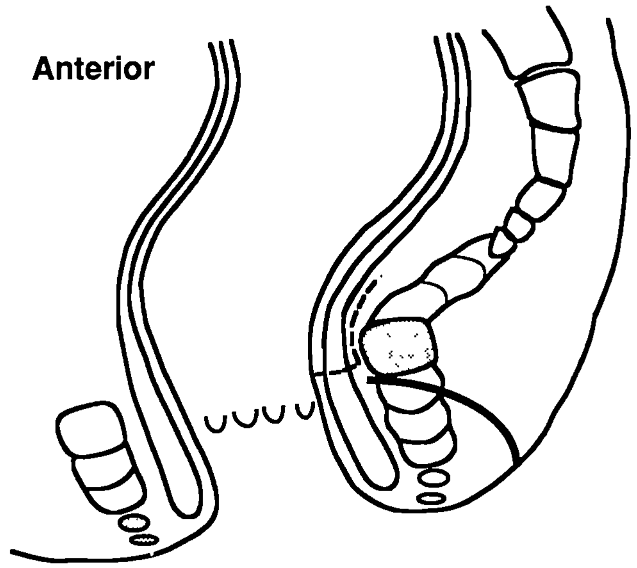

Figure 2 *Sagittal section of the anorectal region showing the 'full thickness' rectal flap*

deterioration in the patient who had impaired continence as a result of a previous 'laying open' procedure. This patient is currently considering a sphincter repair.

Discussion

The treatment of fistulae-*in-ano* by 'laying open' the track was first performed by John of Arderne[1] in the 14th century. The 'laying open' technique has remained standard surgical practice since 80 per cent of fistulae are intersphincteric[2], involving little division of the anal sphincter. Milligan and Morgan[3] claimed that continence was entirely dependent on the integrity of the puborectalis. However, more recent work has demonstrated that continence is also dependent on the extent of division of the anal sphincter[4,5]. Christensen *et al.*[6] reported that even in a series of patients with trans-sphincteric fistulae treated by a seton 'cut through' technique, approximately 50 per cent were rendered incontinent to a varying extent.

The 'laying open' technique is also inappropriate in many patients with fistulae associated with Crohn's disease in whom there is a failure of healing Heller *et al.*[7] suggested that the distribution of Crohn's disease was important in this respect, with a high rate of healing in patients with proximal disease but failure of healing in most patients with colonic involvement. The extent of tissue division is also an important determinant of healing in Crohn's fistulae-*in-ano*[8], with few surgeons prepared to 'lay open' trans-sphincteric fistulae.

The anorectal advancement flap was originally used in the treatment of rectovaginal fistulae[8], but impressive rates of healing have also been reported in patients with idiopathic fistulae-*in-ano*[10–12]. Moreover, in two large series[11,12] , only one of over 200 patients suffered a deterioration in continence. The technique has the additional advantage that recurrence does not preclude a repeat procedure. Moreover, the fistula may still be treated in the orthodox way.

The results of the present study support these findings We believe that the advancement flap should include a full thickness of the rectal wall, since in the anorectal region anastomotic dehiscence is a well recognized problem. Inclusion of the muscular layer of the rectal wall increases the strength and vascularity of the anastomotic site[13], provides a thicker cover for the deep end of the fistulous tract, and should ensure that the flap is less prone to ischaemia Other workers have either incorporated the circular muscle layer in the advancement flap[10,11] or sutured muscle over the internal opening as a separate layer[12] to place the mucosal suture line distal to the internal opening. We question the use of oblique upward incisions from each corner of the internal wound[10–12] This manoeuvre can occasionally cause ischaemic necrosis of the advancement flap[11] and in our experience freeing up half the circumference of the rectal wall enables anastomosis without undue tension. Management of the external component of the tract is also open to discussion. Excision of the tract by 'coring out' may require a shorter period of external drainage and produce more rapid resolution of the fistula[10,11]. However, we believe it would be very difficult to 'core out' a horseshoe track and, moreover, this would leave a very large wound which might take a long time to heal, especially in patients with Crohn's disease Debridement of the tract is an easier procedure and in our experience produces a satisfactory outcome.

Patients with Crohn's disease were excluded from most previous studies using advancement flaps for both rectovaginal fistulae and fistulae-*in-ano*. Whereas many workers avoid anal surgery in patients with Crohn's disease[7,14], others operate only on selected cases[8]. Previous reports of the use of advancement flaps in Crohn's fistulae-*in-ano* have included small numbers of patients with a high recurrence rate[15–17]. Our experience is slightly more encouraging, with complete resolution of the fistula in five of six patients treated, including three patients with proctocolitis.

Consideration of the causes of early recurrence could have important implications in management and case selection. In a patient with a recurrent idiopathic fistula, early removal of the drain (on the fifth postoperative day) may have resulted in recurrent sepsis. Thus in an anorectal advancement flap procedure, external drainage of a fistulous track should probably be maintained for a longer period than suggested by Isbister[18] in the treatment of anorectal abscess.

Encouraged by our previous success and the experience of strictureoplasty where successful operations are carried out in the presence of active disease, we attempted an anorectal advancement flap in a patient with a stricture at the rectosigmoid junction. When this patient presented with a recurrent fistula 2 weeks after operation, sigmoidoscopy revealed florid proctitis. Clearly active Crohn's disease is a contraindication to this type of surgery as suggested by Jones *et al.*[15]. Patients who develop recurrence after anorectal advancement flaps should be managed by a period of seton drainage to control sepsis. It is then possible to repeat the procedure and achieve a successful result at least in the case of an idiopathic fistula

Finally, it is apparent that patients treated with anorectal advancement flaps not only enjoy rapid resolution of their fistulae but require little community medical and nursing support. Furthermore, it was our impression that patients undergoing such surgery experienced little postoperative discomfort. This observation is not surprising considering that the incision and anastomosis are performed in the pain-insensitive part of the anorectal region.

In summary, an anorectal advancement flap technique was used in eight patients with trans-sphincteric fistulae-*in-ano*, with no resulting impairment of continence. Successful resolution of the fistula occurred in six patients, including five patients with Crohn's disease, three of whom had a past history of rectal involvement

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Short note

Br. J. Surg. 1990, Vol. 77, October, 1189–1190

Cholecystectomy through a 5 cm subcostal incision

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The first cholecystectomy was performed by Carl Langenbuch on July 15th, 1882 through a T-shaped incision[1]. The horizontal limb of the incision was parallel to the liver edge and the longitudinal limb ran along the lateral border of the rectus muscle. Since then at least seven further incisions for cholecystectomy have been described[2]. Of these, the most commonly used are the right paramedian and Kocher's subcostal incision. Kocher's subcostal incision is preferred by many surgeons as it is associated with a lower incidence of pulmonary and abdominal complications[3]. The incision extends from the tip of the xiphoid caudally and laterally 5–6 cm below the costal margin into the flank[2] Such an incision varies in length between 15 and 30 cm depending upon the size of the patient, and is recommended for adequate exposure with minimal retraction Improvements in technique enable procedures to be performed safely through smaller incisions; further, ultrasonography can locate the position of the gallbladder, indicating the best site of incision.

The aim of this study was to determine whether cholecystectomy could be performed safely through a 5 cm transverse subcostal incision

Patients and methods

Informed consent was obtained from 55 consecutive patients with symptomatic gallstones. There were six males and 49 females, with an average age of 48 years (range 13–81 years). Patients with clinical or radiological evidence of common bile duct stones were not included in the study. There were no other exclusion criteria. Twenty-seven per cent of our patients were obese, an additional 33 per cent were above the acceptable weight range and 40 per cent were below or within the acceptable weight range for the population[4] Three patients had undergone previous upper abdominal surgery (vagotomy and pyloroplasty in one patient, right hemicolectomy in one, and excision of a hepatic cyst in one) Significant risk factors were present in nine patients (cardiovascular disease in four, pulmonary disease in three and diabetes in two patients).

Pulmonary function studies were performed on patients before operation and on the first and third postoperative days These included vital capacity (VC), forced expiratory volume in 1 s (FEV_1), and peak expiratory flow rate (PEFR) The amount of intramuscular analgesia required after operation for each patient was recorded

Postoperative complications were monitored. Pulmonary complications were considered present when there was clinical or radiological evidence of atelectasis, pleural effusion or pneumonia. Wound infection was recorded when there was clinical evidence of cellulitis or purulent discharge from the wound.

Technique

The gallbladder was localized before operation by ultrasound, and its position marked on the skin All operations were performed under general anaesthesia. A headlight (Quadrilite 4000, Designs for Vision, Inc , New York, USA) was used to provide additional lighting by one author (P J O'D.) A 5 cm subcostal incision was marked over the site of the gallbladder In young patients, muscle was divided, in the elderly, it was split along its fibres and retracted The junction of the cystic and common bile duct was identified first. If difficulty was encountered in identifying anatomical landmarks, the length of incision was extended. Operative cholangiography was performed in all patients through the cystic duct, except in one who had an endoscopic cholangiogram 24 h before operation The gallbladder was removed from the fundus down or the cystic duct upwards depending on the surgeon's preference The cystic duct and artery were ligated with 2/0 polyglactin 910 (Vicryl®, Ethicon, Edinburgh, UK) Specialized retractors were not used[5] Fascia was closed with No 1 polydioxanone (PDS, Ethicon, UK) and skin with subcuticular, 4/0 polyglycolic acid (Dexon®, Davis and Geck, UK) One closed suction drain was left in the gallbladder bed and removed on the first postoperative day Nasogastric tubes were not used All intravenous fluids were discontinued, and patients commenced on free fluids and light diet on the first postoperative day. All patients were reviewed as out-patients 1 month following discharge

Results

Cholecystectomy through a 5 cm subcostal incision was possible in 46 (84 per cent) of the 55 patients Thirty-nine had chronic cholecystitis, four had acute cholecystitis, one had mucocele of the gallbladder, one had empyema of the gallbladder and one had a gallbladder polyp. The average operating time was 61 min (range 30–90 min). The average blood loss was 69 ml (range 20–240 ml). Pulmonary function was significantly depressed ($P < 0{\cdot}01$ for VC, FEV_1 and PEFR) on the first postoperative day, but returned to normal by the third postoperative day.

In seven (13 per cent) patients anatomical landmarks could not be identified satisfactorily through a 5-cm incision and the incision had to be extended The characteristics and operative findings in this group are illustrated in *Table 1.* The average length of incision for this group was 13 cm (range 10–17 cm)

Table 1 *Characteristics of patients in whom incision had to be extended*

Patient no.	Age (years)	Height (cm)	Weight (kg)	Pathology	Anatomy
1	34	160	87	Chronic cholecystitis	Normal
2	33	162	84	Acute cholecystitis	Normal
3	39	155	77	Chronic cholecystitis	Short cystic duct
4	37	165	85	Chronic cholecystitis	Intrahepatic gallbladder
5	68	152	50	Empyema	Normal
6	75	175	83	Mucocele	Normal
7	51	155	70	Chronic cholecystitis	Short cystic duct

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In two patients (4 per cent) the incision was extended to perform a choledochotomy for removal of common bile duct stones.

The average postoperative hospital stay for all patients was 3·9 days (range 1–8 days). The average hospital stay for the group in whom cholecystectomy was possible through a 5 cm incision was 3·5 days (range 1–6 days). This compared with 5 days (range 3–8 days) for those in whom the incision had to be enlarged. Analgesic requirements were not different between the groups and averaged four intramuscular injections per patient.

There were five (9 per cent) postoperative complications, two of which occurred in one patient (wound infections in two, exacerbation of chronic obstructive airways disease in one, congestive cardiac failure in one, and disruption of drain in one patient).

Discussion

This study shows that cholecystectomy can be performed safely through a 5 cm subcostal incision in most patients with symptomatic gallstones. The operation, while technically more difficult in some instances than cholecystectomy through a standard incision, was performed by surgical residents under supervision in 40 per cent of patients. Two surgical assistants were provided for all operations, a Senior and Junior House Surgeon when the operation was performed by a Consultant or Senior Registrar, and a Consultant and Junior House Surgeon when the operation was performed by a Senior House Surgeon or Junior Registrar.

Reduction of abdominal wall trauma by use of short incisions should be accompanied by rapid recovery and short hospital stay for patients. In this study, the average hospital stay was 3·5 days in patients undergoing cholecystectomy through a 5 cm subcostal incision. This compares with a hospital stay of 8·5–11 days for cholecystectomy in other European centres[3,6].

Despite many recent innovations in the treatment of gallstones[7–9], cholecystectomy remains the treatment of choice for symptomatic patients[10]. Current methods of disintegration or dissolution of gallstones, or combinations of both, will have unsatisfactory long-term results as long as a functioning gallbladder with a patent cystic duct remains *in situ*. Experimental work on obliteration of the gallbladder with cystic duct occlusion has met with some success in animal studies[11,12]. While application of this technique could prevent recurrent stone formation in the future, it may not dispel anxiety concerning further complications.

Cholecystectomy through a 5 cm subcostal incision is accompanied by rapid recovery and short hospital stay for patients. Further evaluation of shorter incisions for cholecystectomy is required A prospective randomized trial comparing this incision with a standard subcostal incision for cholecystectomy is under way at our institution.

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Surgical workshop

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Localization of impalpable breast lesions: a new device

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With the current emphasis on early diagnosis of breast cancer using screening mammography, the surgeon is increasingly confronted with the problem of biopsy of impalpable lesions. The characteristics of malignancy may be subtle, and accurate excision of all suspicious mammographic abnormalities after localization is essential. The hook wire is the preferred method of localization, and several variations of this device have been described[1–3]. Although complications are uncommon, wires may be misplaced within the breast at the time of localization[4], or migrate within the breast after localization, or even occasionally transgress into the pleural cavity[5,6], or be transected during surgery[7]. The authors have found that the standard commercially available wires can be dislodged from the breast at the time of biopsy and have had problems in palpating fine wires during surgery, particularly in densely fibrotic breast tissue.

This report describes our experience with a new type of needle, the use of which was found greatly to facilitate localization and excision of impalpable mammographic abnormalities.

Patients and methods

Since 1987, 51 consecutive patients (mean age 48 years, range 37–70 years) have undergone preoperative needle localization using a new device. The mammographic abnormalities requiring biopsy consisted of either an area of microcalcification or impalpable mass lesions. The new device was specifically designed to overcome many of the disadvantages of the commonly used commercially available systems and consisted of two separate parts The first is an 18-gauge two-piece needle consisting of a sharp trocar and a cannula (*Figure 1a*) (Following further modifications a one-piece needle is now available) The second part is an inner cannula preloaded with the localizing guide wire (*Figure 1b*).

Initial positioning was carried out using the two-piece needle and only when its position was optimal was the trocar withdrawn and the cannula with the preloaded localization device inserted into the 18-gauge cannula. The localization wire tip is 'x'-shaped with two forward pointing prongs to arrest any migration into the breast, and two backward pointing prongs which prevent accidental withdrawal (*Figure 1c*). Immediately proximal to the tip there is a stiff 3-cm section of wire designed for easy palpation in the operating theatre The rest of the guide wire consists of standard 0 028 inch (0 07 cm) diameter wire which is flexible and can be easily secured to the skin One additional feature of the device is a radio-opaque clip (*Figure 1a*) which can be attached to the wire at the surface entry point for final check films This helps the surgeon to relate the position of the lesion to the skin entry point

All localizations were carried out immediately before operation in the radiography department using conventional mammography equipment and a compression localization grid The shortest possible route from the skin to the lesion was used and the needle was placed at a depth so that its tip lay at or beyond the lesion when the orthogonal view was obtained. From this view the position of the needle tip could be assessed and adjusted if necessary When the position was judged to be satisfactory, the trocar of the two-piece needle was removed and replaced by the cannula preloaded with the localization device. This was held in place firmly while the wire of the localization device was pushed into the breast The two cannulae were then pulled out while pressure was continued on the localization wire Further films (craniocaudal and mediolateral) were then taken to show the final position of the device. A recent development has been to simplify the device by using a one-piece needle with a preloaded localization device. Both types of needles are now available commercially (X-Reidy breast localization needle, William Cook, Europe A/S, Bjaeverskov, Denmark)

All patients were biopsied under general anaesthesia. The hooked wire was left in place in the excised tissue to help orientate the radiologist and the pathologist. The patient was kept in the operating room until excision of the desired area had been confirmed by specimen radiography

Results

The preoperative localizations were performed by a variety of radiologists and were easily tolerated by all patients In two

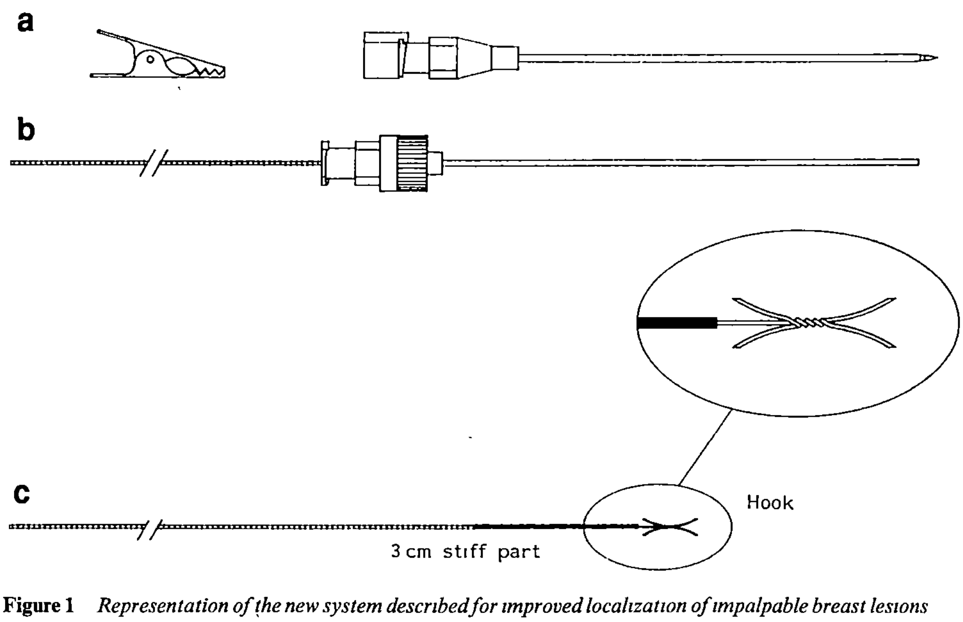

Figure 1 *Representation of the new system described for improved localization of impalpable breast lesions*

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patients with multifocal abnormalities two lesions were localized and excised simultaneously. At biopsy the wire was easily felt, even in dysplastic and fibrotic breasts, and it was readily traceable to the area of excision. There was no evidence to suggest any displacement of the device between the final localization film and surgery. A problem was encountered in two early cases where, following successful introduction, the x-shaped tip became detached from the wire body. Despite this problem the device was retrieved and a satisfactory localization achieved.

Discussion

This report describes our early experience with a new type of needle, the use of which was found to facilitate greatly the localization and excision of impalpable mammographic abnormalities. The greater thickness and stiffness of the wire segment proximal to its tip ensured that it was easy to palpate in the breast at the time of biopsy. Further, the greater thickness of the new wire rendered it less likely to inadvertent transection during surgery. The firm barbs at the end, apart from reducing the possibility of accidental dislodgement, enabled the surgeon to feel the tip easily. The stability enables placement either immediately before surgery or, if necessary, on the preceding day, although we have no experience of the latter. The use of a stereotactic localization unit may facilitate needle introduction but again we have no experience of this. Preoperative introduction of the device was as easily performed using conventional equipment as with the other commercially available wires, provided that the procedure was undertaken by a radiologist experienced in the technique of needle localization. The only problem encountered in this series was the dislodgement of the tip from the main wire in two early cases. This new device has resulted in greater accuracy and ease of excision of all types of impalpable breast leasions.

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Usefulness of anorectal myectomy

Sir

We feel that the conclusions drawn by Pinho, Yoshioka and Keighley (*Br J Surg* 1989, **76**: 1163–4) are unwarranted. In this study, the authors found that only 17 per cent of patients (11/63) with chronic constipation who were treated by anorectal myectomy achieved satisfactory results while as many as 70 per cent (44/63) had outcomes that were poor. Based on these results, and the fact that 10 per cent of their patients (6/63) developed mild incontinence, the authors recommended that anorectal myectomy should no longer be considered in the treatment of patients with chronic constipation.

Patients were chosen for myectomy in this study based on videoproctographic and electrophysiologic evidence of 'outlet obstruction'. Selection criteria used included an inability to expel a 100 ml balloon from the rectum, increased electrical activity in the puborectalis muscle during attempted defecation, and an inability to open the anorectal angle and evacuate contrast during videoproctography. However, several important factors regarding the patient population selected are unclear. The term 'constipation' is never clearly defined. Since no patient had evidence of megarectum and only 28 patients (44 per cent) had abnormal colonic transit studies, one is uncertain of the true degree of symptoms from which these patients suffered. In addition, only 9 patients (14 per cent) had abnormal rectoanal inhibitory reflexes suggesting internal anal sphincter dysfunction.

In reviewing the selection criteria for treating these patients with myectomy, it is not surprising that their overall results were unsatisfactory. This procedure, essentially an extensive internal anal sphincterotomy, has been advocated in the treatment of severe constipation in patients thought to have short segment Hirschsprung's disease. Pinho and associates refer to the favourable results achieved by Martelli *et al.*[1] in the treatment of outlet obstruction, but reviewing this article reveals that Martelli's group performed more than a simple anorectal myectomy. They resected the internal sphincter and additionally included both layers of the rectal musculature posteriorly up to 6 cm above the dentate line.

We feel that the selection criteria in this study largely assess the voluntary mechanism of defecation. Since anorectal myectomy only alters the involuntary mechanisms (i.e. the internal sphincter), it would appear that the poor results in this group of patients is quite predictable. Anorectal myectomy is a procedure with merit when it is utilized in the appropriate clinical setting and should continue to be considered in the therapy of a select group of constipated patients with short or ultra-short segment Hirschsprung's disease.

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Epidural analgesia in colonic surgery

Sir

We read with interest the paper by Bredtmann *et al.* on anaesthetic techniques in colorectal surgery (*Br J Surg* 1990, **77**: 638–42), and in particular their confirmation that anaesthetic technique may influence postoperative bowel function. We believe this principle has wider implications, particularly in those patients undergoing restorative proctectomy.

The widespread adoption of stapling devices for coloanal and low colorectal anastomoses has significantly reduced the incidence of poor postoperative continence which, not infrequently, followed a peranal hand sutured anastomosis. However, continence following low anastomoses may still be a problem if the anal sphincter is weak or damaged. The calibre of the rectum and proximal colon is rarely a limitation to the diameter of the stapling device used, and we routinely employ the 31 mm EEA® stapler (Auto Suture UK, Ascot, UK) in all anastomoses below the peritoneal reflection. However, we have often experienced difficulty in removing the stapler after use because of spasm in the anal sphincter. The problem may be overcome if a smaller stapler is used, but this may lead to stricture formation which is not seen with the 31 mm device. Although the application of forcible traction will deliver the 31 mm stapler without apparent trauma to the anastomosis itself, the possibility of damage to a marginally competent sphincter cannot be excluded if delivery of the stapler is difficult.

Good surgical access is usually achieved during the pelvic dissection by means of a self-retaining retractor, and the anastomosis is thus usually completed at a time of minimal muscle relaxation. We have found that complete relaxation of the sphincter, achieved by the administration of an additional dose of muscle relaxant before insertion of the stapler, facilitates its easy removal after use. We have now been using this technique routinely for 2 years and would recommend its adoption in all colorectal anastomoses employing the large EEA stapling device.

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Recurrent torsion of the testis

Sir

The interesting short paper by Mr O'Shaughnessy and colleagues (*Br J Surg* 1990, **77**: 583) highlights the rare and perplexing development of torsion following orchidopexy for undescended testis; they collected seven such cases. Even more unexpected is torsion of a testis that has previously been fixed specifically to prevent torsion. There are 16 case reports describing this event, i.e. recurrent torsion affecting either the previously twisted organ ($n = 11$), or its innocent fellow ($n = 5$)[1–4]. It is not enough just to explore the opposite hemiscrotum and deal with the tunica vaginalis by eversion, plication or excision. As further security it is necessary to fix both testes to the scrotal wall using non-absorbable sutures (the use of absorbable sutures may be the common denominator in recurrent torsion[1,5]. This combined manoeuvre should ensure the development of permanent adhesions to anchor the testis, and there is no report of recurrent torsion thereafter.

Among 624 Bristol patients with proven torsion, 41 cases occurred in undescended testes (7 per cent), confirming the link between these two conditions[6]. During orchidopexy for undescended testis, it would therefore seem sensible to look for abnormalities such as a high investment of the tunica or partial separation of the epididymis and testis. If these predisposing features are found, the opposite testis should probably be explored and fixed, even if it occupies a normal position in the scrotum.

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Impact of AIDS on surgery

Sir

In his report (*Br J Surg* 1990, **77**. 748) MacGowan suggests that 'all patients who undergo surgery should be regarded as potentially HIV positive' and that surgeons should 'avoid puncturing gloves' and be 'extra careful to avoid self-inflicted injury'

I have yet to meet a surgeon who did not try to avoid self-inflicted injury. If nearly 50 per cent of surgical gloves are punctured, as MacGowan states, then puncture avoidance is clearly a non-starter The true implications of treating every patient as HIV positive are enormous. Routine 'high risk' precautions including disinfection of theatres and equipment between each case would substantially reduce the number of cases on each operating list and and correspondingly increase the cost of surgery and the length of waiting lists.

It is suggested that if a surgeon is contaminated by an HIV positive patient he should be 'kept out of theatre' until repeated HIV tests are negative, but if we truly regard all patients as potentially HIV positive then surely this should apply to contamination by any patient, at least until the patient is shown to be HIV negative Since contamination is such a frequent event, who will be left to do the operating?

Such advice is not merely impracticable and unhelpful but also dangerously misleading It gives the illusion of action while failing to face up to the true implications of the problem Instead, the unfortunate surgeon who contracts HIV while operating will be blamed for failing to 'avoid self-inflicted injury'. This is cold comfort

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Early operative fracture management of patients with multiple injuries

Sir

We found the leading article by Schein and Saadia (*Br J Surg* 1990, **77**· 361–2) raised some interesting points One possible cause for the continuing morbidity and mortality in patients who do not have their long bone fractures rigidly fixed could relate to recurrent episodes of fat emboli. Although the final pathological mechanism by which the emboli cause symptoms is open to debate it has been shown that further movement or manipulation of the fracture site can lead to further showers of emboli. This is suggested by the following.

1. It has been shown that manipulation of a long bone fracture several days after injury can be followed by periods of hypoxaemia This has been monitored in patients over periods of many days when episodes of hypoxaemia followed adjustments of traction and manipulation of fractures. It is unaffected by warfarin anticoagulation[1].
2. Two episodes of clinical fat embolism following multiple bone fractures have been described in the same patient[2].
3. Skin petechiae occur in 'crops', this would be consistent with recurrent showers of emboli[3]

Although patients with multiple injuries requiring intensive care suffer from a whole range of problems described at the close of the article it can be assumed that early internal fixation of long bone fractures prevents movement of the fracture site and this must in part explain the diminution of some of the respiratory and cerebral problems We suggest that if the fat emboli become infected they will contribute to the overall septic state of the patient

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Diagnosis and management of mesenteric infarction

Sir

The leading article by P.-A Clavien (*Br J Surg* 1990, **77** 601–3) concentrates on the need for re-establishing blood flow by reconstructive or clearance technique, as well as reviewing pharmacological aids and cystoprotective therapy.

Whilst acknowledging the difficult decisions in operative assessment of intestinal viability, Dr Clavien omitted comment on anastomotic considerations. Little consideration has been given to the management of the bowel in this situation. Restoration of continuity has traditionally been made using end-to-end anastomosis but considerable benefits can be derived from other anastomotic techniques.

Mesenteric infarction is not the exclusive result of the geriatric population and with neonatal necrotizing enterocolitis the difficulties are often compounded by the multifocal nature of the infarcts. Compromise of intestinal blood flow in this condition makes choice of anastomotic technique particularly important.

Intraluminal pressure has significant influence on anastomotic healing and an end-to-side anastomosis with exteriorization as in the Bishop–Koop method[1] provides substantial benefits in comparison with the traditional end-to-end technique. Effective decompression of the proximal bowel is achieved and this is of particular value in the case of multifocal ischaemia when multiple proximal resections with end-to-end anastomosis are best kept deflated by the ileostomy Moreover, assessment of viability can be simply achieved by inspection of the exteriorized bowel and early stoma closure easily effected once the patient's condition permits More general application of this paediatric technique is recommended.

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Vacuum drainage of groin wounds after vascular surgery

Sir

It was with interest that we read the recent article by Dunlop *et al.* (*Br J Surg* 1990; **77**· 562–3) concerning the use of vacuum drainage in groin wounds following vascular surgery. It is only the second such trial that has been published and like Healy *et al*[1], the authors concluded that drainage should be abandoned Why then have so many surgeons been using such drains in the absence of positive evidence for their benefit? It is probably because suction drainage has a proven role in the management of other procedures such as mastectomy, abdominoperineal excision of the rectum and hysterectomy[2], and that infection of a prosthetic graft is such a disastrous event when it occurs that any measure which might reduce its incidence is attractive.

The first point we would like to raise concerns the fact that drains were left in for only 48 h. Our policy is to ensure that the drain is removed only when drainage has dropped to less than 35 ml in 24 h This often necessitates leaving the drain for longer than 48 h If the drain is removed when larger volumes of fluid are still draining it seems likely that any effect on the incidence of wound collections will be reduced, invalidating this trial We were surprised by the overall incidence of lymphatic discharge from the wounds in their study being 28 per cent (35 out of 127 wounds) Perhaps this would have been less had the drains been left in longer We understand the worry that drains might become infected if left in for too long, but positive cultures probably occur either because of contamination of the drain tip on removal by skin organisms or because of poor nursing technique when bottles are changed In a series by Smith *et al*[3] only 12 of 100 Redivac® tips (Biomet Ltd, Bridgend, UK) removed on the second postoperative day produced a positive culture and only one of these wounds developed an infection with the same organism

What the trials by Dunlop *et al* and Healy *et al.*[1] have done is to document that there is no increased incidence in wound complications following the use of these drains. However, the important question is what might be the effect of vacuum drainage on the incidence of prosthetic graft infection Prosthetic graft infection occurs in

< 5 per cent of cases in modern series[4] and for a trial to reach statistical significance on this point many hundreds of cases would be needed even if drainage did confer a large advantage. This trial is clearly too small to attempt to answer this question We would suggest that the role of vacuum drainage in this situation remains unproven and that the authors' recommendation that drains should not be used is not actually proven by their data. To resolve the point a multi-centre trial will probably be required Until further evidence emerges we feel that vascular surgeons are still justified in using vacuum drainage in groin wounds.

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1 Healy DA, Keyser J, Holcomb GW, Dean RH, Smith BM. Prophylactic closed suction drainage of femoral wounds in patients undergoing vascular reconstruction *J Vasc Surg* 1989; **10**: 166–8.
2. Moss JP. Historical and current perspectives on surgical drainage. *Surg Gynecol Obstet* 1981; **152**: 517–27.
3. Smith SRG, Dawson PM, Greenhalgh RM. Infection and the use of Redivac® suction drains in arterial reconstruction. In: *Extra-anatomic and Secondary Arterial Reconstruction.* R. M Greenhalgh, ed London: Pitman, 1982. 26–34.
4. Moore WS. Infection in prosthetic grafts. In. *Vascular Surgery.* R B Rutherford, ed London. W B. Saunders and Co., 1984, 412–24.

Association of congenital hypertrophy of the retinal pigment epithelium with familial adenomatous polyposis

Sir
Familial adenomatous polyposis is viewed in two ways. Firstly, it is seen as an all-encompassing syndrome within which patients display differing signs as the condition evolves, but where all patients are capable of developing its varied stigmata Alternatively, it is perceived to be a disease separable from that known as Gardner's syndrome. This second approach forms the basis of the paper by Iwama *et al.* (*Br J Surg* 1990; **77**. 273–6), wherein the presence of congenital hypertrophy of the retinal pigment epithelium was sought in patients with and without Gardner's syndrome. In adopting this concept, Iwama *et al.* display its deficiencies.

Although they found that twice as many patients with Gardner's syndrome exhibited congenital hypertrophy of the retinal pigment epithelium than did non-Gardner's patients (91 *versus* 45%), patients were allocted to the Gardner's group on the basis of inadequate foregut examination. Only 36 of 49 patients underwent a foregut investigation, and in some this took the form of a contrast radiograph of the stomach only. We have shown that the duodenum of nearly all familial adenomatous polyposis patients contains polyps[1]. Similar high rates have been reported from Japan[2,3]

Further, we are told that ten patients with desmoid tumours or exostoses were included in the Gardner's group; but we are not told how these manifestations were diagnosed Were all patients screened effectively for these stigmata? If not, then the separation of familial adenomatous polyposis patients into Gardner's and non-Gardner's groups becomes even more equivocal than that implied by the remark by Iwama *et al.* that the definition of Gardner's syndrome is 'obscure'.

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1. Spigelman AD, Williams CB, Talbot IC, Domizio P, Phillips RKS Upper gastrointestinal cancer in patients with familial adenomatous polyposis. *Lancet* 1989, **ii** 783–5
2. Watanabe H, Enjoji M, Yao T, Iida M, Ohsato K Accompanying gastroenteric lesions in familial adenomatosis coli *Acta Path Jap* 1977; **27**: 823–39.
3. Yao T, Iida M, Ohsato K, Watanabe H, Omae T. Duodenal lesions in familial polyposis of the colon. *Gastroenterology* 1977; **73**. 1086–92.

Author's reply

Sir
Drs Spigelman and Phillips misunderstood our paper in several ways. Firstly, I concur that familial adenomatous polyposis is a single entity including so called Gardner's syndrome. Secondly, according to our definition, foregut polyposis is not a feature of Gardner's syndrome Our paper[1] was the first to mention the very high incidence of gastric polyposis in familial adenomatous polyposis patients. We are following up these patients to exclude grastric carcinoma, periampullary carcinoma or desmoid tumour after colorectal surgery Regarding the diagnosis of 'exostosis' or desmoid tumour, it is unlikely that tiny hard humps on the head or fibrous tumours in the back or in the surgical scar will be missed. Naturally, we can not detect small and asymptomatic intra-abdominal fibrous tumours except by chance I stressed in this paper that expression of congenital hypertrophy of the retinal pigment epithelium has a familial tendency and that patients with manifestations of Gardner's syndrome show congenital hypertrophy of the retinal pigment epithelium more frequently than those without

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1 Utsunomiya J, Maki T, Iwama T *et al* Gastric lesion of familial polyposis coli *Cancer* 1974; **34**: 745–54.

Potential hazards of mechanized surgical retractors

Sir
During training as a junior surgeon; I was taught that it was the surgeon's responsibility to ensure the patient is protected from accidental harm during surgery. This included checking that no part of the patient was in contact with the metal parts of the operating table, limb supports, etc to avoid risk of electrical burns to the patient's skin when using the diathermy Enquiries with operating department assistants have confirmed that this insulation of the patient is still emphasized during their training too.

It is disturbing, therefore, to see that several types of mechanized surgical retractors – Omnitract® and now Emeltract® (*Br J Surg* 1990, **77** 133) – are being marketed without any apparent inbuilt insulation I accept that these retractors are usually clamped to the operating table over surgical drapes but I do not feel that this will offer adequate insulation as a small tear or a wet drape will easily allow an electrical circuit to become established between the patient and the table I have been in contact with the manufacturers of the Omnitract system but have not been able to convince them of the inherent risk, all they say is that no incident has yet been reported

Users of the sternal retractor will recall that in the past the manufacturers modified the design of the upright supports to provide a non-conducting end to isolate the patient from the table These replacement supports then had to be purchased at the user's expense.

I would, therefore, urge surgeons who are considering acquiring these undoubtedly useful retractors to consider the potential hazards carefully. Perhaps if others are also concerned the manufacturers could be persuaded to modify the design before too many more are sold.

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Book reviews

Difficult Problems in General Surgery

J. L. Sawyers, L. F. Williams. 266 × 177 mm Pp 526 Illustrated 1989. London Wolfe Medical, £56.50.

This book of approximately 500 pages, written by 52 authors (mostly American) contributing to 30 chapters, provides glimpses into some of the dilemmas and controversies in general surgery By size it cannot be comprehensive Seventeen chapters are devoted to gastrointestinal problems (e g. oesophageal motility, reflux gastritis, etc.) Three chapters refer to vascular problems and the remainder are a miscellany, ranging from parathyroid autotransplantation to the management of reptile and insect bites in the USA Certain chapters were particularly to be commended – those concerning gastric carcinoma, reflux gastritis, the surgical approach to patients with biliary symptoms but without stones, the management of postoperative biliary fistula and stricture and the management of liver trauma and necrotizing fasciitis. The two editors from Nashville seem to have not only attained their goal of providing an updated overview of some controversial issues to the general surgeon but also have produced a comfortable text for candidates studying for higher qualifications to dip into.

Perhaps a modern book concerned with surgical conundrums should have included a discussion on assessment and management of elderly patients undergoing major surgical procedures On the whole, illustrations and tables are clear and there are a comprehensive number of references with each chapter Perhaps a second volume to this edition would be welcome and I feel that it has a worthy place in every medical library.

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An Atlas of Surgical Exposures of the Upper Extremity

R Tubiana, C R McCullough, A. C Masquelet 235 × 350 mm Pp. 359. Illustrated 1990. London Martin Dunitz.

The introduction of modern techniques of microsurgery, reconstructive surgery of joints, conservative resection of tumours with prosthetic replacement and of myocutaneous pedicle flaps in the surgery of the upper limb are just some of the reasons why a detailed knowledge of the anatomy of the upper extremity is required by surgeons working in this area The publication of this large atlas is, therefore, welcomed

Its authors are well equipped for the task. Professor Tubiana is an international name in the surgery of the hand, and his two colleagues, one French and one British, trained under him Leon Dorn, the artist, is already well known in this country for his contributions to Rob and Smith's *Operative Surgery* The *Atlas* has a standard plan. Each approach has an anatomical introduction, followed by notes on indications, position of the patient. the incision and the surgical exposure The illustrations are clear, large accurate drawings, most of which are in colour They are supplemented by cross-sectional anatomical diagrams.

The upper limb is considered systematically from the shoulder to the fingers and includes the thoracic outlet and the supraclavicular brachial plexus. Separate sections deal with exposures of the joints, bones, peripheral nerves and vessels with considerable emphasis, of course, on the hand The final section considers the standard upper limb and latissimus dorsi flaps

This is an atlas that will be welcomed, and much used, by the wide range of surgeons who are concerned with the complex details of the surgical exposures of the upper limb.

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The Theory and Practice of Oncology – Historical Evolution and Present Principles

R W Raven. 300 × 215 mm Pp 355 Illustrated 1990. Lancashire Parthenon Publishing. £55.00 hardback

The pace of development of medicine is such that the student and practitioner sometimes pay too little attention to the lessons of the past. This is nowhere more true than in the study of malignant disease whose academic basis and clinical practice span a multitude of disciplines, some of which are at the most rapidly advancing edge of scientific progress

This work, written by the doyen of UK surgical oncology, sets out to bring together within the scope of a single volume all those facets of the multi-disciplinary activities which collectively comprise oncology The introductory chapters on cancer in antiquity, the early cancer hospitals and the voluntary cancer organizations are fascinating and provide a valuable source of reference both for the professional and lay reader. There follow sections outlining the scope of tumour biology and pathology and the relative roles of surgery, radiotherapy and chemotherapy in combined management. The importance of counselling, rehabilitation and continuing care are recognized in the allocation of separate chapters

This is not a text book and the author has devoted space to matters of special personal interest, e.g. historical landmarks in the treatment of breast cancer, classical surgical operations and the subject of long survival after cancer surgery. By the same token some material must inevitably be thinly spread and the use of space for an appendix describing lymph node anatomy in the context of general coverage could be questioned These points do not detract from the value of this panoramic overview which is beautifully produced and lavishly illustrated by material much of which derives from the author's own collection

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Techniques and Procedures in Critical Care

R W Taylor, J M Civetta, R R Kirby 185 × 232 mm Pp 418 Illustrated 1989 Philadelphia J B Lippincott Company. $95.00 softback.

There is a somewhat disconcerting variety of styles, in this 25 author book, ranging from the folksy approach to rather heavy going narrative in which abbreviations abound Throughout, doctors and nurses are referred to as 'care givers' The book is divided into two parts – techniques and procedures – but it is difficult to find any fundamental difference between the two sections. It opens with a woolly and philosophical chapter on clinical assessment in the intensive care unit, a very basic contribution on aseptic technique at the bedside and a verbose chapter on precautions for care givers. There are better offerings on cardiac output, blood gases, pulmonary function, oxygen therapy and particularly comprehensive contributions on mechanical ventilation and neurological function monitoring. Diverse chapters deal with the practicalities of venous, arterial and pulmonary artery cannulation and monitoring of cardiorespiratory activity, and lead on to advanced airway management, including fibreoptic intubation and bronchoscopy Sadly, the section on cardiopulmonary resuscitation is woefully inadequate, and what they do advise bears little similarity to the American Heart Association guidelines

The best parts of the book are the simple descriptions of techniques. The authors would have done better to concentrate on these and produce a small didactic handbook. Because of the rather muddled layout there is much repetition and the book is neither readable nor valuable for a quick update

It is difficult to define the market Care givers are not an amorphous group and range from the junior nurse to the experienced doctor I am afraid this volume is likely to fall flat between the two stools.

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Endovascular Surgery

W S Moore and S. S. Ahn, eds 190 × 266 mm Pp. 550 Illustrated 1989 London W. B Saunders and Co £64.00 hardback

Many new techniques have been developed over the past few years to supplement and replace conventional reconstructive surgery This book consists of a large number of short chapters each written by a different author addressing the different aspects of these techniques The term 'endovascular surgery' has been coined by the authors but applies as much to radiology as it does to surgery

The first large section is on vascular endoscopy and includes details of the technology and experience of different users in the management of arterial and venous disorders There are useful tips here to be learnt for anyone planning to set up a vascular endoscopy service and the chapter on organization and funding is of particular interest to those who are financially minded

Further sections include chapters on atherectomy devices and there is a good description of the various techniques with guide-lines on indications and contraindications The section on laser systems is quite extensive and includes a useful chapter on laser welding The final section of the book is on adjunctive procedures to endovascular surgery and includes a short chapter on endovascular ultrasound

The range of topics chosen for this book is ambitious in a book of only 550 pages and inevitably suffers as a result. After being somewhat excited at the prospect of reading a new book I found I was disappointed in the rather superficial nature in which many topics were addressed and the almost universal lack of detailed results I was left with the impression that many of these techniques were experimental and that there was almost no hard data to justify their continued use

The book is studded with many black and white drawings and photographs giving good illustration to the text The only exception being angioscopic photographs which are rather disappointing in view of the technology involved. The references were limited in some chapters and many of them were confined to the North American literature

Despite these criticisms the book remains a useful reference for any trainee in vascular surgery or radiology and will undoubtedly find a useful place in the reference library

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Surgery Annual 1990

L M Nyhus 155 × 235 mm Pp 425 Illustrated 1990 Appleton and Lange £58 50 hardback.

Surgery Annual 1990 presents an interesting but disparate series of articles on topics ranging from intestinal glutamine metabolism to the psychological consequences of breast cancer surgery In these times of increasing specialization within general surgery this diversity of subject matter enables surgeons of differing interests to catch up on current topics of relevance and importance to their colleagues in other fields

Recent developments in surgical science are covered both by the aforementioned chapter on the relevance of glutamine metabolism to gastrointestinal integrity and by a comprehensive account of the interactions between malignant cells and the extracellular matrix The reviews covering recent issues in clinical management are generally comprehensive and well written by experts in their fields Topics include acute pancreatitis, Zollinger–Ellison syndrome, nutrition in childhood cancer, incontinence due to anorectal malformations, anorectal motility disturbances, radiotherapy in colorectal cancer, anastomotic aneurysms, BCG in superficial bladder cancer and splenic conservation Those surgeons involved in resource management initiatives will be interested to read of attempts to relate surgical audit to hospital costs in the USA Technical developments such as laser angioplasty and endorectal sonography are introduced to a wider audience, and there are also chapters on surgical techniques including the repair of hypospadias, reversed gastric oesophagoplasty, tissue expansion in reconstructive surgery and the retroperitoneal approach to aortic aneurysms A new feature for the *Annual* is the provision of an 'Overview of surgery' which demonstrates how difficult it is for surgeons to keep track of developments outside their own field, an imbalance which this book aims to redress through its international panel of contributors.

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Computers in Medical Audit – A Guide for Hospital Consultants to Personal Computer Based Medical Audit Systems

West Midland Regional Health Authority in collaboration with Andersen Consulting. 162 × 237 mm. Pp 89 Not illustrated 1990 Oxford Royal Society of Medicine £10 00 paperback

This 89 page softback manual is essential reading for the clinician or manager about to invest in an audit system. It was prepared by a panel of authors from the West Midlands Regional Health Authority and Andersen Consulting They provide a helpful perspective on audit in general and emphasize that a computer system is only one component part of the process. Only two pages are devoted to describing hardware, although a further three (with extensive factual duplication) are found in an appendix In practice it makes sense to choose the software for audit and then, in the light of its requirements, decide upon the hardware platform. This advice is lacking

The chapter on choosing the software contains sound advice The essence of audit is comparison, the argument in favour of uniformity and comparability of systems is made but with little vigour. In systems design there is a conflict between flexibility and comparability A rigidly specified system may not allow the user to change much but comparability is conserved; on the other hand a system may be so 'versatile' that it can do anything but, because it is changeable by the user, it becomes unique and incomparable Twenty-two software systems were identified, of these only nine fulfilled basic minimum criteria for further evaluation The greater part of this booklet is an analysis on those nine systems

The strength of *Which?* reports when undertaken by the Consumers Association is the combination of objective assessment by a panel of experts and 'user feedback' In this case the expert assessment is merely an investigation into what a program will or will not do, not how well it fulfils that task. Although there is a 13 page chapter devoted to user comments it is of limited value because for nine systems the authors received only 14 completed user questionnaires

Notwithstanding these comments, this booklet condenses a great deal of information about the leading audit systems currently available The authors are careful to point out that it was not their intention to recommend a 'best buy', although they do draw some conclusions This guide will help the buyer to draw up a shortlist of systems to evaluate for him or herself

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Benign Breast Disease

J A Smallwood, I Taylor, eds 160 × 240 mm Pp 189 Illustrated 1990 Sevenoaks Edward Arnold £25 00 hardback.

Benign breast disease has always played second fiddle to breast cancer despite the fact that the vast majority of patients presenting to a breast clinic do so with non-malignant conditions This is reflected in research and published papers – *The British Journal of Surgery* published nine papers on benign breast diseases in volumes 75 and 76 compared with 28 with malignant disease as their subject This book is one of two recent UK publications which address the problems of benign breast disease and it does so well. The book took its origins from two meetings held in Southampton and is a good review of current thinking on various aspects of benign disease The 12 chapters cover the problems of benign breast disease and its association with malignancy in a satisfactory fashion, although some repetition does occur and the editorial pen might have been used to more effect The plastic surgery contribution does not sit happily in such a book although the chapter on psychological manifestations is a valuable contribution.

Between this book and the Cardiff competition, the balance of interest in benign breast disease is being redressed and I can recommend it to those who see patients with these conditions.

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Notices and announcements

18 October 1990
Cracking Gallbladders and Bile Duct Problems
London, UK
Information: Charlotte McLeish, The British Institute of Radiology, 36 Portland Place, London W1N 4AT, UK

20–27 October 1990
Operative Arthroscopy
Kauai, Hawaii
Information: UCLA Extension, Health Sciences, PO Box 24901, Los Angeles CA 90024, USA

23–31 October 1990
Clinical Anaesthesia in the 1990s
Bristol, UK
Information. Louise Deakin, Courses Dept, The British Council, 65 Davies Street, London W1Y 2AA, UK

28 October–1 November 1990
42nd Postgraduate Assembly
Honolulu, Hawaii
Information. Ann Singer, Meetings Manager, The Endocrine Society, 9650 Rockville Pike, Bethesda, MD 20814, USA

29 October–3 November 1990
Fourth U.S. Phlebology Workshop in Paris
Paris, France
Information: Walter de Groot, 801 Broadway, Seattle, WA 98122, USA

1–3 November 1990
Carotid Duplex Technology, Hands-On Instruction
Disneyland
Information. Patricia Aguilar, Keith Mauney & Associates, Inc, 600 E Las Colinas Blvd, Suite 250, Irving, Texas 75039, USA

2 November 1990
The Management of Complications Following Vascular Surgery
Newcastle-upon-Tyne, UK
Information: Mr J. Chamberlain, Ward 7 Office, Freeman Hospital, Freeman Road, High Heaton, Newcastle-upon-Tyne NE7 7DN, UK

3–7 November 1990
State of the Art in Digestive Surgery
Delhi, India
Information. Convention Centre, Hotel Taj Palace Intercontinental, Sardar Patel Marj, New Delhi 110021, India

4–6 November 1990
Lower/Upper Extremity Vascular Technology, Hands-On Instruction
Disneyland, USA
Information Patricia Aguilar, Keith Mauney & Associates, 600 E Las Colinas Blvd, Suite 250, Irving, Texas 75039, USA

5–9 November 1990
Annual Course in Hepatobiliary and Pancreatic Surgery
London, UK
Information: Wolfson Conference Centre, Hammersmith Hospital, Du Cane Road, London W12 0NN, UK

13–16 November 1990
2nd International Interdisciplinary Symposium
Vienna, Austria
Information: Peritoneum and Peritoneal Access (PAX), F. Schulz, c/o Vienna Academy of Postgraduate Medical Education and Research, Alser Strasse 4, A-1090 Vienna, Austria

13–16 November 1990
Peritoneum and Peritoneal Access
Vienna, Austria
Information: PAX Secretariat, c/o Vienna Medical Academy, Alser Strasse 4, A-1090 Vienna, Austria

15–17 November 1990
Second International Congress on Access Surgery
The Netherlands
Information: Conference Agency Limburg, Mrs M. Frank-Roovers, University Hospital Maastricth, PO Box 1918, 6201 BX Maastricht, The Netherlands

15–17 November 1990
10th Annual WBAMC Trauma Symposium
El Paso, Texas, USA
Information: Mrs Marty May, Secretary to Maj Stephen D. Carey, Trauma Service/SICU, William Beaumont Army Medical Center, El Paso, Texas 79920-5001, USA

24–27 November 1990
Recent Advances in Anaesthesis, Pain, Intensive Care and Emergency
Italy
Information. Trieste Traduzioni Congressi, 34125 Trieste, Italy

26–29 November 1990
6th International Symposium on Cardiopulmonary Urgencies and Emergencies
Rotterdam
Information: Omar Prakash, Thorax Centre, Erasmus University, Postbus 1738, 3000 DR Rotterdam, The Netherlands

2–5 December 1990
The 7th Asia—Oceania Congress of Otorhinolaryngological Societies
Hong Kong
Information Congress Secretariat, 1/F 57 Wyndham Street, Central, Hong Kong

6–8 December 1990
1st International Symposium on Benign Breast Disease and Chemoprevention of Breast Cancer
Genoa, Italy
Information: Oncologia Clinica, Istituto Nazionale per la Ricerca sul Cancro, Viale Benedetto XV, 10, 16132 Genova, Italy

11–13 December 1990
5th International Workshop on Therapeutic Endoscopy
Hong Kong
Information: Joseph W. C. Leung, Senior Lecturer in Medicine, Prince of Wales Hospital, Shatin, Hong Kong

19–20 January 1991
Hong Kong Surgical Forum
Hong Kong
Information: Forum Secretary, Department of Surgery, University of Hong Kong, Queen Mary Hospital, Hong Kong

27 January–1 February 1991
Second European Winter Oncology Conference
Meribel, France
Information: IMEDEX B.V, PO Box 3283, 5203 DG 's-Hertogenbosch, The Netherlands

22–25 April 1991
4th International Symposium on Cardiovascular Pharmacotherapy
Geneva, Switzerland
Information: ISCP'91, c/o AKM Congress Service, PO Box CH-4005, Basel, Switzerland

4–5 May 1991
5th International Meeting of the Australian and New Zealand Society of Phlebology
Sydney, Australia
Information: Dr G. Mark Malouf, Secretary, ANZ Society of Phlebology, PO Box 2166, North Paramatta 2151, Sydney, Australia

2–14 June 1991
Methods of Immunologic Research and Diagnosis
Buffalo, New York, USA
Information James F. Mohn, Director, The Ernest Witebsky Center for Immunology, 272 Sherman Hall, Buffalo, New York 14214, USA

6–8 June 1991
5th European Congress of the Society for Surgery of the Shoulder and the Elbow
Wurzburg, FRG
Information Prof Dr. med J. Eulert, Orthpadische Universitatsklinik, Konig-Ludwig-Haus, Brettreichstr. 11, 8700 Wursburg, FRG

25–31 August 1991
International Surgical Week
Stockholm, Sweden
Information. Scientific Secretariat, 155, Hauptstrasse 63, PO Box 411, CH-4153, Reinach BL1, Switzerland

SURGERY

CONTENTS, SEPTEMBER 1990
Volume 108 Number 3

Official Publication
SOCIETY OF UNIVERSITY SURGEONS, CENTRAL SURGICAL ASSOCIATION,
and **AMERICAN ASSOCIATION OF ENDOCRINE SURGEONS**

ORIGINAL COMMUNICATIONS

Page 475 **Solid and papillary epithelial neoplasms of the pancreas**
Michael J. Zinner, MD, FACS, Muhammad S. Shurbaji, MD, *and* John L. Cameron, MD, FACS,
Baltimore, MD.

481 **Nonendocrine cancer of the pancreas in patients under age forty years**
Edward J. Ivy, MD, Michael G. Sarr, MD, *and* Herbert M. Reiman, MD,
Rochester, Minn.

488 **Nutritional consequences of total gastrectomy: The relationship between mode of reconstruction, postprandial symptoms, and body composition**
J. Miholic, MD, H. J. Meyer, MD, M. J. Müller, MD, A. Weimann, MD, *and* R. Pichlmayr, MD,
Hannover, Federal Republic of Germany

495 **Carcinoma of the main hepatic duct junction: Indications, operative morbidity and mortality, and long-term survival**
Toshiharu Tsuzuki, MD, Masakazu Ueda, MD, Shigeru Kuramochi, MD, Shuhei Iida, MD, Shin Takahashi, MD, *and* Hisami Iri, MD,
Tokyo, Japan

502 **Intraperitoneal 5-fluorouracil infusion for treatment of both peritoneal and liver micrometastases**
Stephen Archer, MBBS, *and* Bruce Gray, PhD, FRACS,
Perth, Western Australia

508 **Use of homologous platelet factors in achieving total healing of recalcitrant skin ulcers**
Subhash Chandra Atri, MS, MNAMS, Jayant Misra, MBBS, Dipti Bisht, MD, *and* Krishna Misra, PhD,
Allahabad, India

513 **Endoscopic alternatives in the management of colonic strictures**
Mehmet C. Oz, MD, *and* Kenneth A. Forde, MD,
New York, N.Y.

520 **Analysis of 1084 consecutive lower extremities involved with acute venous thrombosis diagnosed by duplex scanning**
Thomas M. Kerr, MD, John J. Cranley, MD, J. Robert Johnson, PhD, Kenneth S. Lutter, MD, George C. Reichmann, BS, Robert D. Cranley, MD, Michelle A. True, BS, *and* Michael Sampson, GN,
Cincinnati, Ohio

528 **Long-term effects of dietary calcium on risk markers for colon cancer in patients with familial polyposis**
Hartley S. Stern, MD, Roger C. Gregoire, MD, Hanoch Kashtan, MD, Jonah Stadler, MD, *and* Robert W. Bruce, MD,
Toronto, Ontario, Canada

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534 **The continuing challenge of burn care in the elderly**
Jeffrey R. Saffle, MD, FACS, Catherine M. Larson, RN, John Sullivan, PhD, *and* Jane Shelby,
Salt Lake City, Utah

544 **Moderate smoke inhalation produces decreased oxygen delivery, increased oxygen demands, and systemic but not long parenchymal lipid peroxidation**
Robert H. Demling, MD, *and* Cheryl LaLonde, BS,
Boston, Mass.

553 **Proglumide inhibits cholecystokinin and meal-stimulated pancreatic secretion and release of pancreatic polypeptide**
R. Daniel Beauchamp, MD, Guillermo Gomez, MD, William H. Nealon, MD, Courtney M. Townsend, Jr., MD, George H. Greeley, Jr., PhD, *and* James C. Thompson, MD,
Galveston, Texas

559 **Molecular biology of circulatory shock. Part II. Expression of four groups of hepatic genes is enhanced after resuscitation from cardiogenic shock**
Timothy G. Buchman, PhD, MD, Deborah E. Cabin, BA, Selwyn Vickers, MD, Clifford S. Deutschman, MD, Elsa Delgado, MD, Marc M. Sussman, MD, *and* Gregory B. Bulkley, MD,
Baltimore, Md.

567 **An experimental assessment of the effect of blood transfusion on susceptibility to bacterial infection**
Susan Galandiuk, MD, Christopher D. George, FRCS, James D. Pietsch, BA, Dann C. Byck, BA, R. Craig DeWeese, MD, *and* Hiram C. Polk, Jr., MD,
Louisville, Ky.

CLINICAL REVIEW

572 **Research into the results of resection of hilar bile duct cancer**
Egge J. Boerma, MD, PhD,
Haarlem, The Netherlands

BRIEF CLINICAL REPORTS

581 **Somatostatin analogue in treatment of coexisting glucagonoma and pancreatic pseudocyst: Dissociation of responses**
A. R. Moattari, MD, K. Cho, MD, *and* A. I. Vinik, MD,
Ann Arbor, Mich.

588 **Primary hyperparathyroidism in a hypothyroid child**
George W. Holcomb III, MD, *and* Leonard J. Perloff, MD,
Philadelphia, Pa.

593 **Esophageal lymphangioma: Case report and review of the literature**
D. Castellanos, J. J. Sebastián, A. Larrad, P. Menchen, C. Senent, J. M. Núnẽz, *and* M. López de la Riva,
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This is a partial listing of September 1990 SURGERY contents

Br. J. Surg. 1990, Vol. 77, November, 1201–1202

Extrahepatic portal vein obstruction

Portal hypertension caused by extrahepatic (syn. prehepatic) obstruction occurs when the site of block is in the portal vein before the blood reaches the liver. In Western countries, such patients comprise 5–10 per cent of all cases of portal hypertension but in developing countries this proportion is higher and may reach 40 per cent[1]. Extrahepatic obstruction is the commonest cause of major upper gastrointestinal bleeding in childhood.

The aetiology of extrahepatic portal vein obstruction in most cases is unknown but the postulated causes include congenital malformation of the portal vein or acquired thrombosis following umbilical sepsis, intraluminal trauma during exchange transfusion, and pylephlebitis following intra-abdominal sepsis. Another older group of patients acquires extrahepatic obstruction due to an increase in blood coagulability, due to changes in the vein wall because of inflammation, or in association with tumours in the liver, bile ducts and pancreas. These older patients have been labelled as suffering from secondary extrahepatic obstruction[2] and their clinical features, management and prognosis depend mainly on their original disease.

Patients with extrahepatic obstruction present mainly with recurrent episodes of massive haematemesis, the first of which usually occurs before the age of 10 and often follows a febrile episode. On examination they have large spleens but the liver is of normal size and consistency. Ascites is a rare finding and occurs in children below the age of five or after a bout of bleeding. The diagnosis of extrahepatic obstruction is easily made given the characteristic clinical features, normal liver function tests and ultrasonography or splenoportovenography which demonstrate, in 90 per cent of patients, obstruction at the site of formation of the portal vein where the superior mesenteric and splenic veins unite. In the remaining 10 per cent of patients the entire portal system is obliterated or obstruction occurs solely in the splenic vein resulting in 'segmental' portal hypertension in the gastrosplenic region. Very few other special investigations are necessary for patient management but other studies on patients with extrahepatic obstruction have shown that they have decreased liver blood flow with a hyperkinetic circulatory state[3], diminished pancreatic function[4] and abnormalities in cell mediated immunity[5].

The management of extrahepatic obstruction is controversial. Some authors have suggested that many children outgrow their disease by adolescence with the formation of more effective collaterals and therefore require only supportive treatment for bleeding episodes until collateral formation occurs. However, the weight of current opinion is that these children do not outgrow their disease and that they require more active therapy. The treatment of an acute episode of bleeding is fairly standard and consists of blood replacement and endoscopic sclerotherapy which controls the bleeding in 95 per cent of cases. In the remaining 5 per cent of cases surgery is necessary. These bleeding episodes are said to be well tolerated but mortality figures of up to 31 per cent[6] have been reported; although these mortality rates may be lower than those found in cirrhotics, they are still fairly substantial. Once the first episode of bleeding is controlled, prevention of recurrence assumes paramount importance and the choice lies between endoscopic sclerotherapy and surgery. Endoscopic sclerotherapy is easily performed, relatively atraumatic and carries a low mortality rate and low incidence of rebleeding[7]. However, the experience with sclerotherapy has been limited to small numbers of patients who have been followed over short periods. The disadvantages of sclerotherapy include the five to 12 separate sittings at three-weekly intervals which may be required to obliterate the oesophageal varices and the life-long follow-up that is required to detect and deal with recurrent varices. The large injury-prone spleens, so common in patients with extrahepatic obstruction in developing countries, are left *in situ*. Further there is some evidence that after endoscopic sclerotherapy bleeding may occur from gastric varices and from congestive gastropathy, sources of blood loss which cannot be controlled readily by endoscopic manoeuvres.

Operations for extrahepatic obstruction, usually consisting of splenectomy and formation of a lienorenal shunt, performed by experienced surgeons also carry low mortality rates of under 1 per cent, fairly low rates of rebleeding (4–7 per cent), and no post-shunt encephalopathy[8,9]. However, in some reports mortality rates[10] have

0007–1323/90/111201–02

reached 29 per cent, the rebleeding rates[11] have reached 68 per cent and the encephalopathy rates have been as high as 22 per cent. The reasons for these discrepancies may lie in differences in surgical expertise, the grouping together of patients with primary and secondary extrahepatic obstruction and definitions of encephalopathy which include children who needed 'psychiatric treatment'. In one report[11], encephalopathy was stated to have followed non-shunt procedures as well. The five-year survival rate of these patients has been reported to be 90 per cent[12].

A patient with extrahepatic obstruction in a developing country is probably best treated by a proximal lienorenal shunt operation performed by an experienced surgeon. It is a safe, successful, one-time treatment particularly suitable for a poor patient who has a long distance to travel before reaching an overcrowded medical centre. Endoscopic sclerotherapy should be reserved for those patients whose veins are not suitable for anastomosis or who have rebled after a shunt operation. In Western countries where sclerotherapy is now being strongly advocated in patients with all forms of portal hypertension including extrahepatic obstruction, these advantages should not be forgotten.

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Br. J. Surg. 1990, Vol. 77, November, 1203–1204

General surgical problems in pregnancy

Abdominal pain in the non-pregnant patient is a common problem which can be produced by both pathological and non-pathological factors. The differential diagnosis and management are only made more difficult during pregnancy when such pain is not only a common complaint but also reported by nearly all women at some time[1].

General surgical problems in pregnancy are relatively uncommon. The incidence of non-obstetrical surgery during pregnancy is approximately 1:500 deliveries[2]. Appendicitis is the commonest cause for non-obstetrical surgery (1:1500–6600 deliveries[3,4]) followed by intestinal obstruction (1:2500–3500 deliveries[5] and cholecystitis (1:1000–10 000 deliveries[2,6]). These figures contrast with the higher incidence of pregnancy specific causes of abdominal pain: for example, ectopic pregnancy (1:300 pregnancies), placental abruption (1:100 pregnancies) and non-pathological/physiological causes (reported in virtually all pregnancies)[1,7]. The relative rarity of surgical problems in pregnancy, however, may lead to potentially dangerous delays in diagnosis and management[8]. Of course, the corollary is that obstetrical causes of acute abdominal pain in a woman of reproductive age may be similarly overlooked. Delays in diagnosis and management of general surgical problems in pregnancy can result from changes in the pattern of symptoms and signs produced by the normal anatomical and physiological adjustments occurring during pregnancy. Anatomical changes are particularly evident once the pregnant uterus becomes an abdominal organ at the end of the first trimester, growing to occupy most of the abdominal cavity by term (37–42 weeks). Two important clinical effects of this uterine growth include displacement of the appendix above the iliac crest (producing displacement of pain and tenderness above MacBurney's point), and separation of viscera from the anterior abdominal wall (producing reduction/ elimination of somatic pain).

Pregnancy also has an effect on the pathogenesis of certain conditions. For example, where the intra-abdominal anatomy is abnormal, as in patients with adhesions from previous surgery (including stoma operations), there is an increased risk of intestinal obstruction, especially during the third trimester and early puerperium[5]. Localization of intra-abdominal inflammatory conditions is considered to be impaired in pregnancy by restriction of the omentum's mobility, by the enlarging uterus and possibly by the inhibition of adhesion formation by Braxton Hicks' ('practice') contractions[3]. During pregnancy there has also been reported accelerated growth of gallstones, which has been claimed to result in an increased incidence of clinical cholecystitis[8]. While this latter point has been disputed[6], gallstones are accepted as the commonest cause of acute pancreatitis in pregnancy[8]. The increased risk of symptomatic urinary infection due to a variety of pregnancy related factors, including urinary stasis, is well known and pyelonephritis is the most important renal cause of abdominal pain in pregnancy (1–2 per cent of pregnancies)[1,9]. It is claimed that patients with active inflammatory bowel disease at the time of conception or who develop the condition during pregnancy find that the problem is exacerbated by the pregnancy[10,11]. In contrast, peptic ulceration is apparently ameliorated during pregnancy[8].

Both physiological and pathological clinical features in pregnancy can be shared with certain general surgical conditions. Physiological changes which can lead to this confusion include nausea, vomiting, heartburn, water-brash, constipation and frequency of micturition. In late pregnancy, it is important to differentiate colicky abdominal pain due to a general surgical problem from labour[5]. Pathological conditions related to pregnancy which can add to the clinical dilemma include ectopic pregnancy (lower abdominal pain, often unilateral), haemorrhage into or torsion of an ovarian cyst (lower abdominal pain, often unilateral), red degeneration of fibroids (abdominal pain which is variable in site, severity and duration), placental abruption (abdominal pain of variable severity and site and not necessarily associated with vaginal bleeding) and fulminating pre-eclampsia (epigastric pain). These points should always be remembered when taking the history and examining a female patient and certainly a complete gynaecological and obstetric history should never be omitted. Because of the potential dilemmas outlined, the ideal approach is for both disciplines to be involved if the diagnosis is in doubt. In general, it is only in the first trimester that surgeons will be faced with a pregnant patient who has not seen an obstetrician.

The normal laboratory investigations are appropriate for evaluation of the pregnant patient with a possible general surgical problem but some alterations of normal ranges must be remembered. While serum transaminase and amylase values approximate to those of the non-pregnant woman, the alkaline phosphatase concentration rises markedly and the total protein and albumin concentrations fall slightly. There is a small but consistent fall in electrolyte values which is not of clinical relevance, whereas the urea concentration falls to a value about 25 per cent below the normal non-pregnant level. Pregnancy is normally associated with a

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marked leucocytosis from the first trimester so that values up to 16 000/μl can be encountered. After delivery values up to 25 000/μl can be seen. Ultrasonography is a valuable tool in pregnancy in the evaluation of possible general surgical problems. It is able to identify gallstones and renal pathology (such as calculi and excessive ureteric dilatation) and may be used to diagnose intestinal obstruction and appendicitis. In the first trimester laparoscopy has proved invaluable to the obstetrician in making a diagnosis and avoiding laparotomy; perhaps more surgeons should consider adding this procedure to their range of skills. There is a natural reluctance in pregnancy to use abdominal radiographs, yet their use must be considered when faced with an ill patient who possibly has intestinal obstruction and where delay in diagnosis and management may be dangerous. Furthermore, the hazards of single plain radiographs of the maternal abdomen should not be exaggerated. For example, the risk of teratogenesis from radiation associated with such a diagnostic radiograph (approximately 0.20 rads) is extremely small and it appears that doses have to exceed 10 rads before there is a significant risk[12].

The treatment of general surgical conditions in pregnancy tends to be conservative in the first instance since laparotomy carried an increased risk of miscarriage. This is especially so in the first trimester although this risk is considerably reduced in most planned procedures carried out in the second trimester[2,13]. Preterm delivery and technical difficulty are problems encountered when laparotomy is carried out in the third trimester[13]. However, whilst the risks of surgery during pregnancy should not be minimized, it is the surgical condition requiring operation and not the surgery itself that is the more important factor in influencing maternal and fetal risk[2]. This is well illustrated by appendicitis occurring during pregnancy. When perforation has occurred then the rates for maternal and fetal mortality rate are 17 per cent and 43 per cent respectively. In contrast, both rates are virtually zero if there is no perforation[4]. Performing elective appendicectomy at laparotomy or during caesarean section in pregnant women[3] and cholecystectomy in the second trimester in women with gallstones[13] are controversial prophylactic measures.

Finally, the two 'take-home' messages when faced with a woman with abdominal pain are, first, that obstetricians should remember general surgical conditions and, second, that surgeons should remember pregnancy.

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Pancreatic ischaemia in experimental acute pancreatitis: mechanism, significance and therapy

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Much clinical and experimental evidence suggests that pancreatic ischaemia in the early phase of acute pancreatitis is important in the development of pancreatic necrosis. While depletion of intravascular volume has often been assumed to be the main circulatory defect, an additional disturbance of pancreatic microcirculation has been demonstrated experimentally. Possible contributory mechanisms include chemical-induced vasoconstriction, direct injury of vessel wall, intravascular coagulation and increased endothelial permeability resulting in pancreatic oedema, haemoconcentration and impaired venous drainage. Pancreatic ischaemia as a consequence of these local effects seems to be responsible for the transition of mild pancreatitis to parenchymal necrosis. In experimental models the beneficial effect of various drugs and of sympathetic blockade has been ascribed to an improvement in pancreatic perfusion. Although effective volume therapy is generally accepted as the mainstay of conservative treatment in acute pancreatitis, the efficacy of different fluid preparations is still controversial, and simple fluid resuscitation has not been shown to prevent the development of parenchymal necrosis. The specific impairment of pancreatic microcirculation cannot be prevented merely by replenishment of intravascular volume with crystalloids, albumin or plasma despite normalization of macrohaemodynamics. In contrast, partial replacement of blood by dextran preparations has been shown to increase pancreatic perfusion by improving blood fluidity. Isovolaemic haemodilution in conjunction with conventional fluid therapy may provide a new and effective means of protecting the pancreas from secondary injury due to the early ischaemic phase of acute pancreatitis.

Keywords: Pancreatitis, microcirculation, pathophysiology, drug therapy, haemodilution

For decades acute pancreatitis has been viewed primarily as an injury caused by the uncontrolled unleashing of activated pancreatic enzymes which proceed to autodigest the pancreas and its surroundings. Whereas the site of injury has traditionally been considered to be the pancreatic interstitium, a recent focus has been on primary intracellular events. These considerations have directed attention in the experimental laboratory to the processes of enzyme synthesis, intracellular transfer, secretion and activation, and to possible methods of interrupting these pathways in order to reduce the undesired end-product. It seems fair to say that the resulting efforts have not thus far been fruitful. While some enzyme-based approaches have a demonstrable effect in certain experimental models, none have translated effectively to human disease.

There is now a burgeoning interest in the vascular factor in acute pancreatitis. Necrosis of pancreatic and peripancreatic tissue is increasingly recognized as a key element in the evolution of the disease from mild to severe. The question posed is whether that necrotizing injury is caused by enzymes or ischaemia. Although there is some work showing decreased blood flow to the pancreas in pancreatitis, and even some benefit in attempting to block the decrement, the ideas generated have not been widely taken up. In the following review, we examine the significance of blood flow changes and current approaches to enhancing protection of the pancreatic microcirculation in acute pancreatitis.

Ischaemia as an initiating or aggravating factor in acute pancreatitis

In dogs, haemorrhagic-necrotizing pancreatitis can be produced by intra-arterial injection of 8-20 μm microspheres which irreversibly obstruct terminal arterioles. Use of larger particles results only in pancreatic oedema, probably because obstruction of larger, more proximal vessels allows collateral flow[1]. There is no evidence that temporary complete or partial ischaemia of the pancreas for up to 1 h can alone cause haemorrhagic necrosis. In such experiments, slight histological[2] and functional changes were completely reversible[3-5]. On the other hand, it has been repeatedly shown that ischaemia superimposed upon pancreatic oedema leads to the development of necrotizing pancreatitis. While temporary arterial obstruction alone did not injure the pancreas, following induction of oedematous pancreatitis by duct ligation and hyperstimulation, arterial occlusion for only 15 min resulted in the formation of parenchymal necroses[3,6]. Similar changes have been noticed when the pancreas was subjected to ischaemia before further measures were implemented[7]. Temporary ischaemia seems to render acinar cells more susceptible to degradation by enzymes[7] that are constituents of the pancreatic oedema[8].

There is also clinical evidence for a pathogenetic relationship between splanchnic hypoperfusion and acute pancreatitis. At autopsy, a significantly higher incidence of acute pancreatitis, pancreatic necrosis or abscess was demonstrated in patients dying after oligaemic shock if the shock was severe, as reflected by concomitant renal tubular necrosis compared with patients without accompanying renal changes[9]. In addition, acute pancreatitis after cardiopulmonary bypass operations seems to be associated with intraoperative hypoperfusion in the splanchnic area. Progression of the generally mild course of the disease has been correlated with an additional reduction of cardiac output in the postoperative period[10].

Impairment of pancreatic microcirculation in acute pancreatitis

Changes in pancreatic microcirculation during acute pancreatitis are well documented. Most studies have utilized a model using bile or trypsin injection into the pancreatic duct. The non-specific detergent effect of sodium taurocholate and bile acids in general seems to be responsible for the initial changes due to the immediate dissolution of cell membranes[11,12]. After 1–3 h a second stage in the course of biliary pancreatitis is characterized histologically by the appearance of autophagic vacuoles indicating that enzymatic autodigestion is the mechanism for further parenchymal injury[13]. In many studies indirect methods were applied to assess microvessel function (*Table 1*). Imaging of the pancreatic microvasculature was achieved by intra-arterial injection of methylene blue[16], India ink[17,19] or polymerizing agents[19,21]. In the areas of pancreatitis, vasoconstriction of the proximal segments of the intralobular arterioles was a prominent finding 3 h and 24 h after induction[17,19]. In contrast, vasodilatation was encountered in less affected regions indicating the non-homogeneous distribution of focal ischaemia[21]. These results were further supported by the demonstration of a reduction in pancreatic perfusion using the rubidium-clearance technique[15,18] As depicted in *Table 1*, the time points in the course of pancreatitis at which the results of the various studies were obtained are extremely variable. Segmental spasms of lobular arteries and veins were reported by Thal[14] to occur 5 min after induction of pancreatitis followed by stasis at 15 min. In contrast, using intravital microscopy we found an impairment of the pancreatic microcirculation beginning 30 min after the induction of biliary pancreatitis, with only single capillaries remaining perfused after 3 h[25]. The different time course of changes can be explained by the high intraductal injection pressure in Thal's study, resulting in an increased leakage of bile and a more generalized distribution in the interstitial space. By means of radioactive microspheres Becker *et al.*[23] and Knol *et al.*[24] also confirmed the development of the microvascular failure between 30 and 60 min after the induction of biliary pancreatitis. Becker *et al.*[23] showed a depletion of high energy phosphates in the pancreas in parallel with the impaired nutritional flow, thus emphasizing the physiological significance of pancreatic ischaemia in acute pancreatitis

Table 1 *Survey of previous studies on pancreatic microcirculation during acute pancreatitis*

Author	Species	Methods	Time after induction of pancreatitis	Findings
Thal[14]	Rabbit	Intravital observation	5 min 15 min 20 min 3 h	Spasm of interlobular vessels Capillary stasis Haemorrhage Similar changes
Papp *et al* [15]	Dog	Rb-86 extraction	24 h	Decrease in pancreatic bloodflow, MAP and CO (disproportionate)
Anderson *et al* [16]	Dog	Intra-arterial methylene blue	1 h	Increase of capillary permability (histology)
Anderson and Schiller[17]	Dog	Intra-arterial India ink (histology)	30 min	Reduction of arterial perfusion (histology)
Goodhead[18]	Dog	Rb-86 extraction	20 h	Pancreatic blood flow increased in oedematous, decreased in haemorrhagic pancreatitis; disproportionate reduction of CO and MAP
Papp *et al* [19]	Dog	Intra-arterial India ink and polyvinyl chloride	3 h 12 h	Vasoconstriction of arteries and intralobular arterioles; no capillary filling, AV shunts (histology)
Pissiotis *et al.*[20]	Dog	Venous outflow	10 min to 6 h	Decrease of pancreatic blood flow and BP (proportion?)
Schiller and Anderson[21]	Dog	Intra-arterial silicone rubber	24 h	Constriction of intra- and interlobular arterioles, vasodilatation in less affected areas (histology)
Donaldson *et al* [22]	Dog	Arterial flow probe	15 min to 3 h	Decrease of pancreatic blood flow (disproportionate)
Becker *et al* [23]	Dog	Flow probe, radioactive microspheres, 15 μm	30 min to 2 h	Decrease of pancreatic blood flow, MAP and CO (disproportionate)
Knol *et al* [24]	Dog	Flow probe, radioactive microspheres, 15 μm	1–4 h	Decrease of pancreatic blood flow and CO (disproportionate), no change in shunt perfusion
Klar *et al* [25]	Rabbit	Intravital microscopy	30 min to 3 h	Decrease of capillary perfusion

BP, blood pressure; CO, cardiac output; MAP, mean arterial pressure, AV, arteriovenous

Pathogenesis of capillary stasis in acute pancreatitis

Several lines of evidence indicate that vasoconstriction has an important role in the pathogenesis of pancreatitis. Using the bile model, Gilsdorf *et al.*[26] were able to convert a mild oedematous pancreatitis to haemorrhagic necrosis in cats by electric stimulation at the hypothalamus in order to increase sympathetic activity. In biliary pancreatitis, the evolution of necrosis from pancreatic oedema could be suppressed by postganglionic sympathectomy[27].

There is great support for the concept that solutions which are injected into the pancreatic duct to induce biliary pancreatitis exert their effect via the interstitial route[17,28,29]. Even at a low injection pressure of 40 cmH_2O, rupture of the ductoacinar junction is detectable with subsequent distribution of extravasated juices in the interstitial space, where they gain access to the pancreatic microvasculature[30] precipitating vascular spasm[14] There is also pronounced damage to the pancreatic vessels resulting in haemorrhage, endothelial detachment and thrombosis, as has been shown with the taurocholate, trypsin, and trypsin-digested blood models[13,31,32]. The vasotoxic effect of these substances was further substantiated by the demonstration that interstitial injection into the omentum precipitates similar changes at the injection site[31].

Haemoconcentration and intravascular coagulation play an additional role in the development of pancreatic ischaemia in acute pancreatitis An increase in microvascular permeability is the initial feature of experimental biliary pancreatitis[25,33]. Even if the systemic haematocrit is maintained at the initial level[25], local haemoconcentration takes place at the site of plasma sequestration. In conjunction with the damaged endothelium[13] intravascular coagulation occurs and causes a further decrease of blood fluidity. These changes are aggravated by a systemic hypercoagulability in acute pancreatitis, probably due to thromboplastic material[34] and activated trypsin[35] gaining access to the systemic circulation. Fibrin deposits have been detected in pancreatic capillaries by electron microscopy[36].

Oxygen radicals have been shown to take part in the development of acute pancreatitis[37]. Besides disintegration of cell membranes by lipid peroxidation, free radicals trigger the extravasation of granulocytes into the surrounding parenchyma representing an early lesion in acute experimental pancreatitis The initial margination of granulocytes in the capillaries may be a contributing factor in endothelial damage and impairment of capillary perfusion[37].

An increase in interstitial pressure as a consequence of obstructed lymph drainage further interferes with pancreatic microperfusion due to the impairment of venous outflow[38,39]. During the first hour of pancreatitis Anderson *et al.*[16] demonstrated an increase of thoracic duct lymph flow followed by a pronounced and prolonged reduction Erythrocytes originating from pancreatic interstitial haemorrhages were shown to enter and obstruct the microlymphatics.

Since acute necrotizing pancreatitis is often associated with circulatory shock, great efforts have been made in the past to distinguish specific changes in pancreatic perfusion from secondary mechanisms introduced by general cardiovascular dysfunction. Studies in which the reduction of pancreatic capillary or total blood flow was found to be disproportionately greater than the reduction in cardiac output lend credence to specific mechanisms of microcirculatory impairment[8,22–24] Furthermore, it has been shown that a decrease in pancreatic perfusion cannot be prevented merely by adequate fluid therapy using Ringer's solution even though cardiovascular parameters are stabilized at the baseline level[40]. The analysis of a study in which pancreatic hypoperfusion was prevented by crystalloids alone reveals that the administered volume exceeded clinical relevance (67 ml/kg per h for 5 h)[41]. In this situation, haemodilution associated with the extensive volume replenishment may be regarded as the main mechanism of protection[42].

Therapeutic approaches to pancreatic ischaemia in experimental pancreatitis

The beneficial effect of adequate fluid resuscitation on the systemic circulation in acute pancreatitis is well established. Recently, Horton and Burnweit[41] and Martin *et al*[43] demonstrated in dogs that impaired systemic haemodynamics can be normalized by vigorous fluid replacement in the early stage of experimental acute pancreatitis. On the other hand, stabilization of macrohaemodynamic function does not prevent the deterioration of pancreatic perfusion[40]. Similarly, in mice subjected to diet-induced (choline-deficient, ethionine-enriched) pancreatitis, vigorous hydration with intraperitoneal saline produces increased survival but not biochemical or morphological improvement of pancreatitis[44].

Many studies have been directed at defining the optimal fluid preparation. Because of major differences in study designs with regard to timing, amount and duration of the fluid administration[22,24,44–52], comparisons of these studies are difficult. Furthermore, in some of them the fluid to be tested was added to the basic infusion regimen used in the control group without accounting for the extra volume or the difference in oncotic pressure[22,45,49,51,52].

Despite the different study designs, certain tendencies can be outlined which are reflected by the majority of investigations. If detectable, the beneficial effect of crystalloids was very limited when compared with colloids in terms of survival[47,48,52], histological changes[48,52], pancreatic blood flow[18,22,24,50] and oxygen consumption[51]. Improvement in survival by the administration of crystalloids alone was only registered when compared with untreated control animals and was therefore attributed to the replacement of intravascular volume[44,45].

Most recently, hypertonic saline in combination with hyperoncotic dextran has been shown to increase pancreatic perfusion in porcine septic shock[53]. A redistribution of intracellular and interstitial fluid into the vascular space is considered the main mechanism resulting in a reactivation of organ microcirculation due to a reduction of endothelial swelling. In acute biliary pancreatitis, a concomitant effect on systemic haemodynamics is reflected by the fact that the volume of crystalloids necessary to sustain blood pressure and cardiac output was reduced by 75 per cent following the intravenous administration of 4 ml/kg per h of hypertonic saline–dextran during the initial stage of the disease[54].

With the use of canine plasma as an intravenous substitute, pancreatic blood flow was only improved transiently[22] or remained unchanged in dogs[46]. In a model of severe pancreatitis, mortality could be reduced to some degree with volume replacement by plasma infusion[52]. Rats receiving human albumin fared better than control animals without fluid therapy if the administration was started at the induction of pancreatitis[55], but human albumin failed to improve survival in relation to normal saline in dogs[47]. However, fluid therapy in the latter study was started 8 h after induction of pancreatitis. Albumin administration in an isolated pancreas' preparation reduced the severity of pancreatitis, a protective effect ascribed to an increase in intravascular oncotic pressure[56].

In contrast to other fluid preparations, a beneficial effect of both low and high molecular weight dextran (i.e. dextran 40 and dextran 60/70) in the treatment of experimental acute pancreatitis has been documented repeatedly[18,22,42,45–48,50–52]. A specific effect of dextran on the pancreatic microcirculation can be deduced from different observations Whereas pancreatic perfusion is not influenced when low cardiac output is corrected by plasma[22], treatment with dextran 70 improves both cardiac output and pancreatic perfusion[50]. Furthermore, the administration of dextran 40 results in improvement of pancreatic blood flow even when the cardiac output is not restored[22,46]. Most studies comparing dextran with crystalloids show the dextrans to be superior with respect to pancreatic perfusion[18,22,24,50] and oxygen consumption[51], as well as histological changes[48,52] and survival[47,48,52]. However, Knol *et al.*[24] were not able to demonstrate an improvement of pancreatic perfusion or oxygen consumption by continuous infusion of dextran 40 They concluded that in other investigations which supported a favourable effect of dextran the fluid administration in the control groups was inadequate and suggested a minimum of 6·5 ml/kg per h of crystalloid to allow for adequate comparison

We also found in a model of bile-induced pancreatitis in rabbits that the identical volume was required to maintain cardiovascular stability[42]. Using this model, we performed isovolaemic haemodilution by exchanging whole blood for dextran 60 to reduce the haematocrit to 30 per cent within 5 min. Study of the pancreatic microcirculation by intravital microscopy showed a significant improvement of pancreatic capillary perfusion, correlating with a limitation of parenchymal destruction[57].

In general, the beneficial effect of dextrans on the pancreatic microcirculation can partly be ascribed to antithrombotic properties, which have been demonstrated experimentally[58–60] and clinically[61–64], preventing intravascular coagulation precipitated by low flow conditions and trypsin-induced epithelial damage[29,32,36] Isovolaemic haemodilution *per se* exerts further beneficial effects on the microcirculation. Despite the acute reduction in the number of circulating erythrocytes, oxygen supply is maintained during haemodilution due to a reduction in blood viscosity with a subsequent increase in cardiac output[65] in conjunction with an enhancement of red cell velocity in the microvessels[66] and of flow motion in the capillaries[67,68] The latter compensatory mechanisms are more pronounced in ischaemic tissue areas counteracting low perfusion pressure, margination of leucocytes, and the impairment of capillary flow[69]. Following haemodilution a more homogeneous distribution of nutritional organ perfusion has been demonstrated in various splanchnic organs, particularly in the pancreas[70].

Most recently it has been demonstrated in skeletal muscle that post-ischaemic leucocyte endothelium interaction, particularly leucocyte sticking in post-capillary venules, can be prevented or reduced by haemodilution with dextran, but to a significantly lesser degree when haemodilution is performed with hydroxyethyl starch[71,72]. This observation may lend further credence to a specific effect of dextran on microcirculatory impairment in general. Furthermore, a reduction in leucocyte margination and extravasation in conjunction with a lesser degree of pancreatic oedema has been demonstrated as an effect of haemodilution with dextran 60 in acute pancreatitis[73].

Various drugs have been tested for their effects on pancreatic microcirculation. Vasopressin decreases blood flow to the normal pancreas by 45–83 per cent[20,74,75] but its administration in acute biliary pancreatitis unexpectedly seemed to reduce mortality[76] It was realized later that the apparent benefit was due to the experimental design: vasopressin maintained pancreatic blood flow in the treated group by stabilizing the aortic pressure, which was allowed to fall in the control group[20] Perhaps the greatest attention has been paid to the effect of corticosteroids on pancreatic blood flow Chronic administration of large doses of cortisone results in a significant absolute increase of pancreatic perfusion[74], but concomitant hyperplasia of the pancreas limits the interpretation of these data. Acutely, pancreatic blood flow in acute pancreatitis is improved by both low- and high-dose corticoid administration without influencing blood pressure or cardiac output[77]. It was speculated that this effect results from counteraction of vasoconstrictive substances. In follow-up studies improved survival and a reduction in the severity of acinar lesions was achieved by steroid administration in biliary[78] and in shock-induced pancreatitis[79] More than 30 years ago, a number of reports purported to show that corticosteroids were beneficial in severe pancreatitis in man[80–83] However, since these data were obtained in non-randomized trials and since corticosteroids have subsequently been reported to cause pancreatitis[84–86], steroids have not gained a therapeutic role in acute pancreatitis

The beneficial effect of postganglionic sympathectomy in canine acute pancreatitis was explained by a documented increase in pancreatic perfusion[27]. However, the effect of paravertebral splanchnic block in man was shown to be too limited to warrant the pain and hazard involved in the procedure[87]. The more practicable epidural block did not influence the overall course of the disease experimentally or clinically[88].

Peritoneal lavage combined with volume therapy using crystalloids has been demonstrated to prevent reduction in pancreatic perfusion during experimental acute pancreatitis as compared with volume replacement alone[89]. However, the relevance of this finding with regard to histological changes or survival was not assessed. Lankisch *et al.*[90] demonstrated that continuous peritoneal dialysis reduces peripancreatic fat necrosis without affecting the pancreatic injury itself The major therapeutic mechanism of peritoneal lavage is probably the removal of toxic substances, inflammatory mediators, vasoactive amines and activated enzymes from the peritoneal cavity before they can be absorbed into the systemic circulation[90–93]. Experimentally, the beneficial effect seems to be independent of the degree of additional intravenous fluid administration[55,89,93]. Clinically, no effect could be demonstrated on overall mortality[94,95]

Clinical implications

Treatment in patients with acute pancreatitis is usually not started within the first 8–24 h, i.e. until the patient presents himself for medical care By that time considerable haemoconcentration has often developed due to reduced fluid intake in conjunction with extravascular fluid sequestration. At this stage the deficiency in intravascular volume may amount to up to 30 per cent of total blood volume, the result being general circulatory failure[16]. As suggested by the outlined experimental data, there is a specific disturbance of the pancreatic microcirculation characterized by heterogeneous and low capillary blood flow and increased blood viscosity. Pancreatic ischaemia may develop to a degree which could convert an initially oedematous condition into progressive necrosis.

Rapid restoration of fluid losses has long been recognized as a main therapeutic goal[96–98]. However, fluid replenishment to normalize central venous pressure and to reverse haemoconcentration usually requires at least several hours. Furthermore there is no evidence that fluid therapy with crystalloids, based on stabilization of blood pressure and cardiac output, prevents pancreatic and peripancreatic tissue necrosis. The experimental data cited above suggest that isovolaemic haemodilution with dextran 60/70 could prove to be more effective in preventing tissue necrosis than conventional fluid regimens.

Since the isovolaemic exchange of whole blood for dextran does not adversely affect systemic haemodynamics, the therapeutic effect of dextran can be implemented within minutes. The acute reduction of red cell concentration and thereby oxygen carrying capacity of the arterial blood is compensated by an increase in cardiac output and organ blood flow as a result of the enhanced blood fluidity[65,66]. At a haematocrit of 30 per cent the optimal compromise is reached between the two factors[99]. The volume which needs to be exchanged to accomplish the projected drop in haemotocrit is calculated from a nomogram according to the patient's weight and body length[100], along with the assumption of a mean premorbid haematocrit of no higher than 43 per cent. The withdrawn blood is stored and can be retransfused if desired later. Blood coagulation is not impaired by doses of dextran 60/70 up to 1·5 g/kg body-weight[101]. This upper limit, amounting to 1750 ml of a 6 per cent solution in a 70 kg man, will only rarely be reached

The clinical practicability of isovolaemic haemodilution is under scrutiny and so far has yielded promising results in an ongoing study including 12 patients with moderate to severe pancreatitis (E. Klar, unpublished observations). Ultimately, a randomized controlled trial will be required to establish its therapeutic value.

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Preoperative cytology and mammography in patients with single-duct nipple discharge treated by surgery

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Microdochectomy has been the routine management for single-duct nipple discharge. Our review of 176 consecutive patients surgically treated between 1975 and 1988 revealed eight patients with in situ *carcinomas and seven with infiltrative carcinomas. Seventeen patients had multiple papillomas, two had atypical hyperplasia and two had atypical epitheliosis. Case selection for surgery has recently been advocated. In our study, nipple discharge cytology was helpful in 67 per cent of cases with underlying malignant pathology. Mammography was found to be unreliable, alerting suspicion in only two of 15 cases.*

Keywords: Nipple discharge, microdochectomy, cytology, mammography

Nipple discharge accounts for 3–5 per cent[1,2] of all breast symptoms and is due to various pathologies. Single-duct nipple discharge carries more importance than discharge from multiple ducts. The former is usually caused by a localized lesion, benign or malignant, while the latter is usually the manifestation of a generalized involutionary change in the breast or endocrine abnormality. Conventionally, the management of single-duct nipple discharge is surgical[3,4]. Recently it has been suggested that a more conservative approach be adopted with selective operation only in cases suspicious of a sinister pathology as judged by non-invasive investigations[2,5]. The aim of this study was to review the pathological findings in our patients treated by surgical intervention and to assess the sensitivity and specificity of nipple discharge cytology and mammography in the detection of malignant disease

Patients and methods

Between 1 January 1975 and 31 December 1988, approximately 840 patients with nipple discharge attended the Fulham Road, London branch of the Royal Marsden Hospital. Only 176 patients undergoing surgery were reviewed, those whose sole presentation had been a serous or bloody single-duct nipple discharge. They were operated on because their discharge had been either blood stained or persistent. Patients who had an associated mass palpable in the breast were managed on the merit of the mass and were excluded from this study, as were patients with a clear discharge or multiple-duct discharge

All patients had preoperative cytological examination of the nipple discharge (reviewed by P.T.) and xeroradiography or mammography (reviewed by D.M K). The pathological diagnoses were also reviewed (C.F) and analysed in relation to the patients' ages using the unpaired Student's t test. The pathology was compared with the result of the nipple discharge cytology and mammography. Where a primary breast malignancy arose, the predictive value was assessed

Results

Over the 14-year study period, 176 patients underwent microdochectomy. The mean age was 45 years (range 18–77 years). The mean duration of symptoms at presentation was 10 weeks. One hundred and nine patients (62 per cent) reported a blood-stained discharge at some stage, while 67 patients (38 per cent) had a persistent serous discharge. The patient characteristics and histological diagnoses are shown in *Table 1*. Fifteen patients (9 per cent) had malignant pathology with a mean age of 56 years, while 161 patients had benign pathology with a mean age of 45 years. This difference in age distribution is not statistically significant. Eighty per cent of carcinomas occurred in those patients aged above 47 years, while 70 per cent of benign lesions occurred in those patients below this age.

Of the 15 patients with malignant disease, seven had a non-invasive intraduct carcinoma, one had lobular carcinoma *in situ*, six patients had an infiltrative ductal carcinoma, and one had an infiltrative lobular carcinoma together with an intraduct carcinoma. In this group of patients, mammography was reported to be suspicious in only two cases, one of which proved to be an intraduct carcinoma and one an infiltrating carcinoma. The only other suspicious mammogram was of a patient who had coexistent duct ectasia and papillomatosis. Mammography detected calcification in only two of eight patients with malignancy where it was evident histologically. These data show that mammography had a sensitivity of 13 per cent and a specificity of 99 per cent in detecting carcinoma. Its Youden's reliability index[6] was 0·13

The results of nipple discharge cytology in patients with cancer and high-risk benign lesions is shown in *Table 2*. Ten of the 15 patients with malignant disease had suspicious or positive cytology. Conversely, five patients with normal cytology proved to have a carcinoma and seven patients with benign pathology also had suspicious cytology. Cytology had a sensitivity of 67 per cent and a specificity of 96 per cent with Youden's index of 0·62 in cancer detection. Of the seven patients with suspicious cytology, four patients had duct papillomas, one had atypical lobular hyperplasia and one had epitheliosis with atypia. Only one patient with suspicious cytology had a

Table 1 *Pathological results and patient characteristics*

Histological diagnosis	No of patients	Mean age in years	Percentage with blood-stained discharge
Carcinoma	15 (9)*	56 (30–78)†	53
Atypical ductal/ lobular hyperplasia	2 (1)	62 (61–63)	50
Intraduct papilloma	78 (44)	48 (23–79)	64
Duct ectasia	31 (18)	49 (23–73)	
Fibrocystic disease	25 (14)	40 (18–58)	58
Epitheliosis	2 (1)	44 (41–47)	
Inflammation	14 (8)	37 (24–56)	
No specific diagnosis	9 (5)	43 (23–60)	
Total	176 (100)	45 (18–79)	62

Values in parentheses are *percentages and †ranges

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Table 2 *Histological breakdown of malignant and higher risk groups and their relationship to nipple discharge cytology*

Histological diagnosis	No.	No with epitheliosis		No with malignant or suspicious cytology
		Without atypia	With atypia	
Carcinoma				
Non-invasive	8	1	0	7
Infiltrative	7	1	0	3
Atypical hyperplasia				
Ductal	1	0	1	0
Lobular	1	0	1	1
Papilloma				
Solitary	61	1	1	3
Multiple	17	6	2	1
Epitheliosis only	2	0	2	1

lesion (inflammation) not regarded as a risk factor for malignant disease.

Postoperative complications were minor and limited to one wound infection, one patient with excessive bruising, and five patients with recurrent single-duct nipple discharge requiring further surgery Thirteen of the patients with malignant pathology remain disease-free after a mean follow-up of 5·5 years (range 1–13 years). One patient developed metastatic axillary lymphadenopathy soon after diagnosis and one patient died from cerebral metastasis presenting after 4 years Neither of these two patients was detected by cytology or mammography

Discussion

Conventionally, the management of single-duct nipple discharge is surgical. The most important indication for operative intervention is to exclude a carcinoma. Recently a more conservative approach has been advocated with surgery reserved for selected cases[2,5]. Some have tried to correlate the type of discharge with its pathological cause by attempting to distinguish between a blood-stained and serous discharge[3,7–9]. Several studies[1,10,11], including our own, have failed to find a good correlation between a blood-stained discharge and malignancy, which may also be associated with a serous discharge[4,12] The macroscopic presence of blood-stained fluid is not always supported by the cytological identification of erythrocytes

Locker *et al*[5] suggested using mammography to detect breast malignancies associated with single-duct nipple discharge but its utility was limited in our study, as in others[4,13] despite the fact that eight carcinomas were noted to have microcalcification by the pathologist. Mammography detected only two of these lesions. This may be due to the large earlier proportion (80 per cent) of patients who underwent xeroradiography, a technique now regarded as inferior, compared with film mammography (20 per cent of patients). The impact of modern radiographic techniques may improve the detection of malignancy.

Cytological examination of the discharge has been recommended[9,14–16] and our study confirms its usefulness, alerting suspicion to underlying malignancy in 67 per cent of cases. Furthermore, six out of seven patients with suspicious cytology had benign pathology considered to be a risk factor for the development of malignancy[17–20]

The frequency of malignancy of 9 per cent is comparable to that previously reported[2,5], although the proportion with infiltrative carcinomas (47 per cent) was higher than that of other studies which found 25 per cent[2] and 35·5 per cent[5]. Our pathological review reclassified two *in situ* carcinomas as atypical hyperplasias and two of the infiltrative carcinomas showed only minimal infiltration.

Seventeen patients (10 per cent) had multiple papillomatosis and two patients (1 per cent) had epitheliosis associated with atypia. Both of these conditions are considered to carry a higher risk of developing carcinoma[17–19] and require follow-up. Eighteen per cent of our patients had duct ectasia and it is possible that these patients had a discharge from more than one duct.

Ninety-seven per cent of patients had their symptoms alleviated without recurrence. Apart from identifying 9 per cent of patients with malignancy, a further 12 per cent were found to have a higher risk of malignancy and were followed up, enabling 79 per cent of patients to be discharged. Our results show that mammography is unreliable in diagnosing those patients with malignancy as a cause of single-duct nipple discharge. Cytology is useful but not accurate enough to allow a selective approach, especially in the older age group. Microdochectomy is cosmetically acceptable and effective in alleviating symptoms and has the advantage of providing histological confirmation of the underlying lesion

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Microdochectomy for discharge from a single lactiferous duct

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Microdochectomy for persistent discharge from a single lactiferous duct was performed in 162 women. Invasive or in situ *ductal carcinoma was diagnosed in 16 patients (10 per cent), none of whom had a palpable lump. The discharge was blood-stained in 14 of these women and in two it was clear. Mammography was performed in 15 of these 16 patients and was abnormal in only five. Three patients had atypical ductal hyperplasia, one of whom subsequently developed an invasive ductal carcinoma. Microdochectomy for persistent discharge from a single lactiferous duct is curative and gives a diagnosis of the cause. It remains the treatment of choice whether the discharge is blood-stained or clear.*

Keywords: Microdochectomy, nipple discharge, breast neoplasm

Microdochectomy is the conventional treatment for patients with persistent discharge from a single lactiferous duct. It has been our policy to recommend the operation for such a discharge because it facilitates an accurate histological diagnosis of the cause and abolishes a troublesome symptom. However, a recent report[1] has suggested it is safe to observe such patients provided there is no palpable abnormality of their breasts and their mammograms are normal. We believe this alternative policy is unwise and present our experience to support the traditional view.

Patients and methods

During the years 1979–1988 microdochectomy was performed in 162 women with persistent discharge from a single lactiferous duct.

All operations were performed under general anaesthesia. The orifice of the affected duct was identified by expressing a drop of discharge. A lacrimal probe was inserted and gently passed peripherally as far as possible into the duct. The direction of the lacrimal probe was used as a guide to make a radial incision which encompassed the orifice of the duct on the summit of the nipple and extended across the areola and onto the breast for a short distance. The affected duct was carefully dissected to preserve adjacent ducts. The defect created beneath the areola was closed, or a suction drain inserted as necessary, and the skin was approximated with interrupted fine sutures. The external orifice of the excised duct was marked with a suture to orientate the specimen.

The case notes of each patient were examined for the duration of symptoms, colour of discharge, pain in the affected breast, clinical, mammographic and histological findings, and any complications of surgery. Blood-stained discharge was defined as the presence of bright red bleeding rather than brown discolouration.

All mammograms to the end of February 1988 were performed using Phillips Mammomat equipment (Phillips Medical Systems, Warrington, UK) exposed onto Min R film (Kodak Ltd, Manchester, UK), craniocaudal and true lateral views being taken. After this date an IGE Senograph 600T (IGE Medical Systems Ltd, Stockport, UK) was used in conjunction with Ortho M (Kodak Ltd) film. In addition a mediolateral oblique view replaced the true lateral in order to obtain better definition of the axillary tail of the breast. All mammograms were reported by a consultant radiologist with an interest in diagnostic imaging of the breast.

Results

The mean age of patients was 47·9 years (range 14–79 years). The mean duration of symptoms was 8·2 months (range 0·5–192 months).

The main symptoms and clinical findings are documented in *Table 1*. The mean duration of symptoms in patients with blood staining was 6·5 months (range 0·5–60 months), and in those with clear or coloured discharge 11·6 months (range 1–192 months).

The types of discharge are correlated with the histological diagnosis in *Table 2*.

The accuracy of mammography (91 per cent), which was performed in 129 patients, is shown in *Table 3*. It was inaccurate in 12 patients. Ten patients with normal mamograms had malignancy (i.e. false negative); two had invasive carcinoma and eight ductal carcinoma *in situ*. Two patients in whom mammography suggested malignancy had benign changes (i.e. false positive), although one with atypical ductal hyperplasia presented 5 years later with an invasive ductal carcinoma of the breast.

The mean age of patients with invasive ductal carcinoma was 62 years (range 56–73 years) and the mean duration of their symptoms was 3·25 months (range 2–6 months). The mean age of those with carcinoma *in situ* was 53 years (range 31–79 years) and they had symptoms for an average of 4 months before presentation (range 1–12 months). A significant difference exists between the mean(s.d.) age at presentation of patients with malignant disease (60·3(11·3) years) compared with that of patients with benign disease (46·6(13·4) years) ($P<0.001$, Student's t test).

Table 1 *Presenting symptoms and signs in patients with single duct nipple discharge*

Type of discharge	Discharge only	Discharge +pain	Discharge +lump	Discharge +pain +lump
Blood-stained ($n=104$)	68 (13)	23 (1)	11 (0)	2 (0)
Clear ($n=41$)	28 (2)	6 (0)	5 (0)	2 (0)
Coloured ($n=17$)	14 (0)	2 (0)	1 (0)	0 (0)
Total ($n=162$)	110	31	17	4

Numbers in parentheses indicate numbers of malignancies

Table 2 *Histological diagnosis and nature of discharge in 162 patients undergoing microdochectomy*

Histology	Type of discharge Blood-stained	Clear	Coloured
Invasive duct carcinoma	5	1	–
Ductal carcinoma *in situ*	9	1	–
Atypical ductal hyperplasia	1	2	–
Intraduct papilloma:			
Single	24	11	–
Multiple	6	4	–
Duct ectasia	36	11	12
Fibrocystic change	23	11	5
Total	104	41	17

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Table 3 *Results of mammography applied to the detection of malignant disease in patients presenting with single duct nipple discharge*

Mammography compared with histology	No of patients
True positive	5
False positive	2
True negative	112
False negative	10
Total	129

Discussion

Discharge from the nipple may be the presenting symptom of an endocrine disorder or local disease of the breast[2]. A milky discharge from multiple ducts of both breasts usually has an endocrine cause. Discharge from a single duct usually indicates pathology within the breast. When a patient presents with a discharge from a single lactiferous duct and a palpable mass in the breast, the mass should be excised and sent for histological examination.

Controversy surrounds the management of a patient with discharge from a single duct without a palpable mass. The conventional treatment, particularly when the discharge is blood-stained, is the operation of microdochectomy. In this study all the patients with carcinoma and abnormal mammograms, nine of the ten patients with carcinoma and normal mammograms, and one of the three patients with atypical ductal hyperplasia presented with blood-stained discharge. However the absence of overt blood staining in a discharge does not exclude malignancy, since one patient with invasive carcinoma and one with ductal carcinoma *in situ* had both clear discharge and normal mammograms.

There is controversy over the significance of intraduct papillomas as precancerous lesions[3]. The majority view is that a single papilloma is not precancerous but multiple papillomas may become malignant[4]. In this study 35 patients had a solitary intraduct papilloma and ten patients had multiple intraduct papillomata. Twenty-four of the former and six of the latter presented with a blood-stained discharge; the remainder had a clear discharge. Mammography was normal in all these patients.

It has been suggested that in patients with discharge from a single duct and no palpable lesion, a normal mammogram may preclude surgery[1]. Our experience does not support such a policy. Ten patients with normal mammograms had invasive or *in situ* carcinoma. Had we pursued an expectant policy there would have been delay in diagnosis and treatment for two-thirds of malignancies. Furthermore, two patients with normal mammograms and atypical ductal hyperplasia would have remained unaware of their increased risk of developing carcinoma of the breast, at least four times that of age-matched women from the general population[5]. Unfortunately one of these patients presented 5 years later with an infiltrating duct carcinoma in the same breast. A previous study has suggested that the incidence of carcinoma in patients with single duct discharge and no palpable mass increases progressively with age[6]; our study supports this finding.

The majority of our patients (90 per cent) had benign lesions and no patient with coloured discharge had malignancy. Nevertheless we must emphasize that mammography failed to detect two-thirds of malignancies. In part this may be due to lesions situated in ducts immediately deep to the nipple and areola, an area where the interpretation of mammograms may be difficult. It is of note that the incidence of false positive and false negative mammograms was equally distributed over the 10-year period of this study.

In conclusion, we believe all patients with a persistent blood-stained or clear discharge from a single lactiferous duct should be treated by microdochectomy regardless of the mammographic findings. It abolishes a troublesome symptom, facilitates a definite histological diagnosis of the cause and in our hands is an operation with no mortality and minimal morbidity.

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Fine needle aspiration biopsy in the diagnosis and management of fibroadenoma of the breast

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Cytological and histological biopsies were obtained on 75 breast lumps clinically diagnosed as fibroadenomas. Of these, 95 per cent of lesions were benign. In 51 (68 per cent) confirmed as fibroadenomas histologically, cytology was benign in 78 per cent, but inadequate for diagnosis in 16 per cent. The remaining 24 lesions included three breast cancers and one lymph node with Hodgkin's disease. In this group cytology was inadequate for diagnosis in 54 per cent, including one breast cancer. No lesion with benign cytology was subsequently shown to be malignant. The study supports the view that clinical diagnosis and cytology are accurate in the diagnosis of benign breast disease of this type. Breast cancer may rarely present with the clinical features of a fibroadenoma and too few lesions have been studied to assess fully the performance of cytological biopsy in detecting these small mobile lesions. A non-excisional policy should therefore include prolonged follow-up and repeat biopsy.

Keywords: Breast, biopsy, cytology, fibroadenoma

Excision biopsy of persistent, discrete breast lumps is usually advised because carcinoma cannot be excluded on clinical grounds alone. There is a growing pressure to reduce the number of benign breast lump excisions from patients because of the cosmetic aspects of breast biopsy (which may be repeated or multiple), and from surgeons because of diminishing resources. This is particularly so for fibroadenomas since they occur in young women. They may be multiple and are held to be easy to diagnose, characteristically presenting as mobile, well defined, painless, smooth swellings, clearly demarcated from surrounding breast tissue. With growing experience of fine needle aspiration biopsy (FNAB) in breast disease, it has been suggested that a benign biopsy report on such a lump might justify conservative management[1,2]. We have performed a prospective study of the correlation between clinical diagnosis, cytology and histology of fibroadenomas to assess the value of FNAB in their management.

Patients and methods

During a 15-month period all patients presenting to the breast clinic with a discrete lump which was mobile, painless, smooth and clearly demarcated from surrounding tissue were assessed by the same surgeon. The above criteria were used to diagnose fibroadenoma at the first attendance. A single FNAB was carried out on consenting patients by the same surgeon using a hand-held 10 cm^3 syringe with a 19 gauge needle, making several passes through each lump in different planes. Smears were air dried, stained with May–Gruenwald–Giemsa and reported by the same two cytologists. Aspirates were reported as malignant, suspicious, atypical, benign or inadequate for diagnosis. No attempt was made to diagnose categories of benign breast disease. All patients were advised to have lump excision. Specimens were fixed and examined using haematoxylin and eosin stains. At the end of the study all histology was retrospectively reviewed by another pathologist. The cellularity of each fibroadenoma was graded into one of three categories on a semiquantitative assessment of the epithelial and stromal elements. Typical examples of each grade are shown in *Figure 1*.

Results

Seventy-four patients were seen with lumps fitting the diagnostic criteria. Twelve (16 per cent) had more than one mass. There were 93 lumps in total; FNAB was obtained on 75, and 82 were excised for histology. Both FNAB and histological biopsies were obtained on 75.

Accuracy of clinical diagnosis

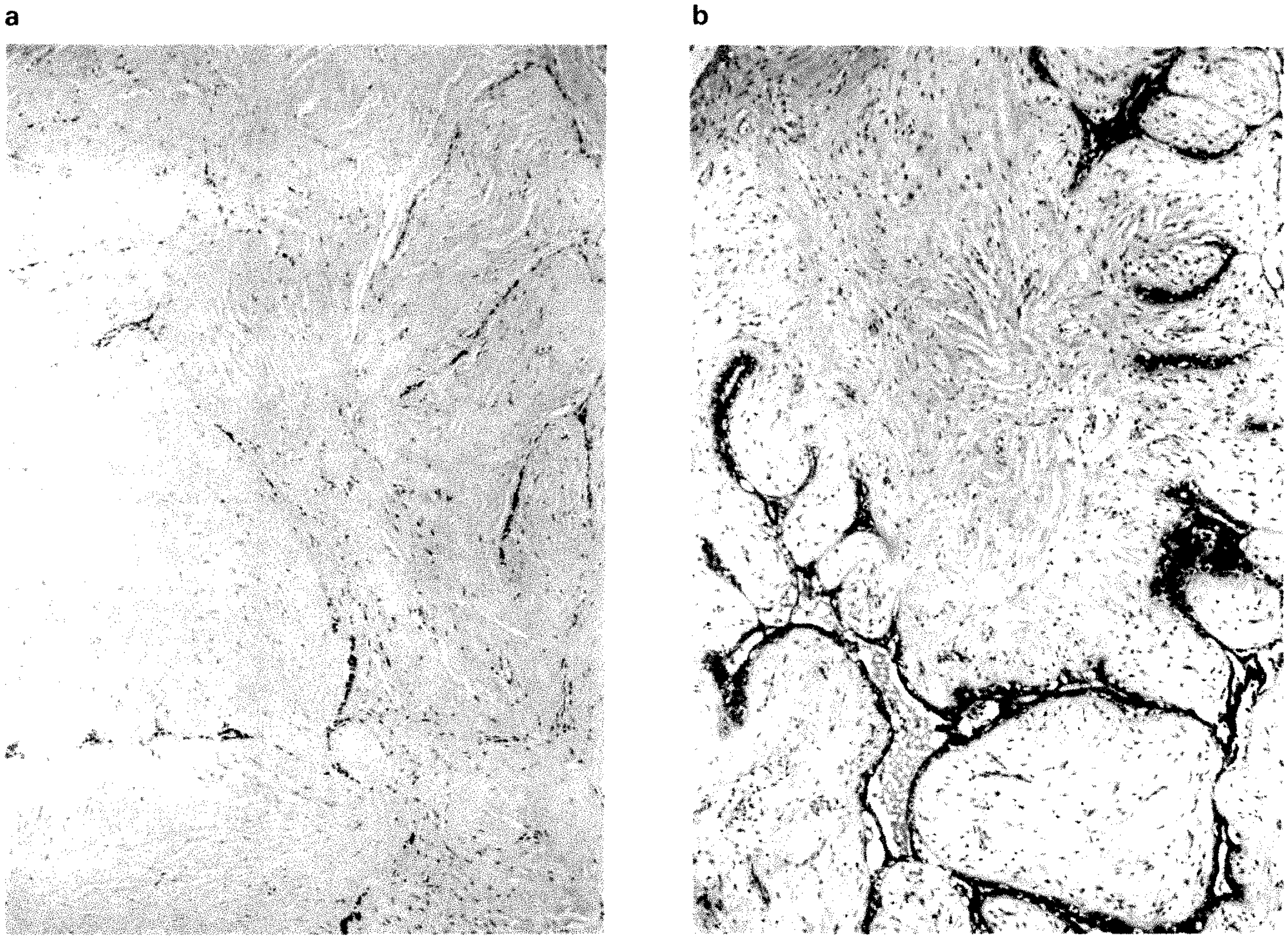
Fifty-one lesions were confirmed as fibroadenomas histologically, and 24 were given other histological diagnoses. The accuracy of diagnosis by a single surgeon specializing in breast disease was 68 per cent. The histology of the lesions which were not fibroadenomas is shown in *Table 1*. Four (5 per cent) of the lesions were malignant. The ages of patients with fibroadenomas ranged from 16 to 38 years (mean 24 years). The patients with ductal carcinoma were aged 46 and 47 years. The patients with the unusual carcinoma and Hodgkin's disease were both aged 21.

FNAB results

Lesions confirmed as fibroadenomas. Of the 51 lesions 40 (78 per cent) were reported as benign. Three (6 per cent) showed

Table 1 *Histology of lesions fitting the diagnostic criteria which were not fibroadenomas*

Breast disease	No. of cases	Non-breast disease	No. of cases
Benign			
Cystic disease	6		
Duct ectasia	2		
Epitheliosis	3		
Adenosis	4		
Lactational	1		
Fat	2		
No significant abnormality	1		
Phylloides tumour	1		
Total	20		
Malignant ductal carcinoma			
in situ	1	Hodgkin's disease in lymph node	1
invasive	1		
unusual microglandular	1		
Total	3		1



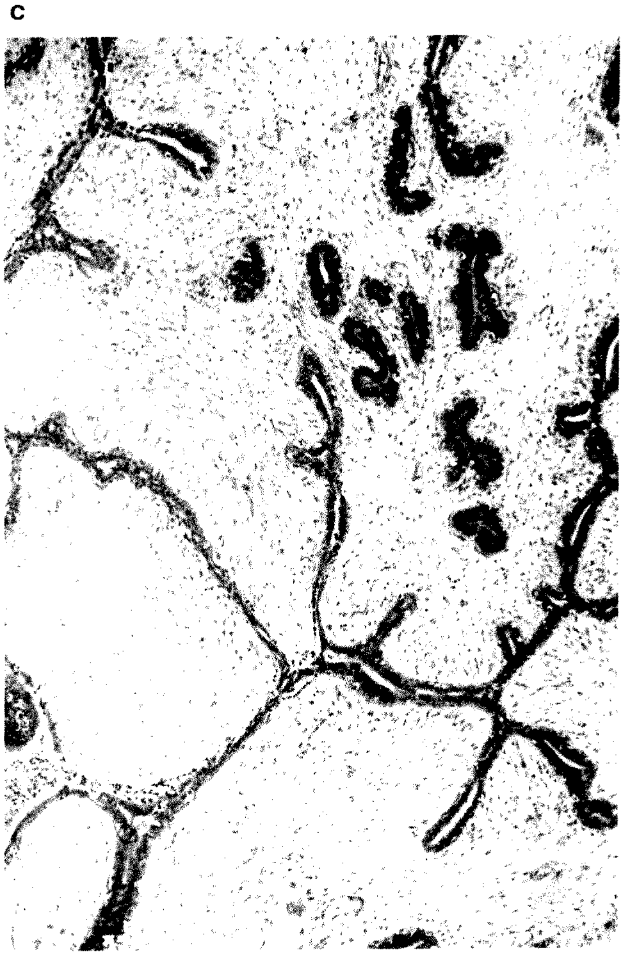


Figure 1 *Cellularity of histologically diagnosed fibroadenomas:* **a** *typical low-cellularity lesion,* **b** *typical moderate-cellularity lesion, and* **c** *typical high-cellularity lesion*

Table 2 *Relationship of cellularity of lesions to cytology report in histologically diagnosed fibroadenomas*

	No. of cases				
Grade	Benign	Atypia	Suspicious	Malignant	Inadequate
I	9	0	0	0	0
II	19	2	0	0	6
III	12	1	0	0	2
Total	40	3	0	0	8

atypia and eight (16 per cent) were inadequate. None was reported as suspicious or malignant. The relationship between cytology and cellularity of the lesions is shown in *Table 2*. There is no apparent relationship between the cellularity of the lesion and the likelihood of obtaining an inadequate biopsy.

Lesions other than fibroadenomas. Of the 24 lesions, nine (38 per cent) were reported as benign, one (4 per cent) as suspicious, one (4 per cent) as malignant, and 13 (54 per cent) were inadequate. Of the three carcinomas one was reported malignant, one suspicious and one inadequate. In the patient with Hodgkin's disease FNAB showed lymphoid cells reported as benign. Thus in this small sample FNAB identified 50 per cent of malignant lesions. There was a higher proportion of inadequate biopsies in this group than in the histologically proven fibroadenomas. No lesion with a benign cytology report was histologically malignant.

Discussion

The results of this study suggest that clinical diagnosis of fibroadenoma of the breast is inaccurate but 95 per cent of lesions fitting the conventional diagnostic criteria of fibroadenoma are benign. In women under 40, 97 per cent of such lesions were benign. FNAB gave a benign result in 65 per cent of the lesions (78 per cent of the histological fibroadenomas) and all were histologically confirmed. Thus a combination of clinical and cytological criteria of benign disease would give a very high level of confidence allowing a conservative policy for women who desire it, or allocation of a relatively low waiting list priority to those accepting surgery.

Of the four malignant lesions, three would have been recommended for urgent excision because of FNAB results reported as malignant, suspicious and lymphoid tissue. In the fourth lesion, an unusual microglandular carcinoma in a 21-year-old, FNAB was inadequate for diagnosis. There were many inadequate biopsies in this series (28 per cent overall; 16 per cent for true fibroadenomas, and 54 per cent for the other lesions). The quality of FNAB specimens depends on the operator, the architecture and cellularity of the lesion and its size. All our biopsies were performed by the same experienced operator. In our series, the number of inadequate biopsies did not appear to relate to the cellularity of those lesions confirmed as fibroadenoma. Most of the lesions were small. It is generally accepted that it is more difficult to obtain good specimens from small lesions, including breast cancers. In the Edinburgh Screening Study it was found that positive cytology was obtained from <50 per cent of 2 cm breast cancers, but >60 per cent of 3 cm cancers[3]. It may not be possible to improve the quality (and hence the predictive value) of fine needle biopsies in these relatively acellular benign lumps.

This study supports the recommendations of others that a benign FNAB supporting a clinical diagnosis of fibroadenoma, based on strict criteria, could justify conservative management[2]. If delayed reporting of a single biopsy is used, many patients will have inadequate biopsies. In most hospitals, resources do not allow immediate reporting by a cytopathologist in the clinic, facilitating immediate repeat of inadequate biopsies. A conservative policy based on clinical criteria alone, thereby accepting a 5 per cent risk of malignancy, is unacceptable. It remains to be seen whether repeat FNAB of these relatively small acellular lesions can improve diagnostic yield. If not, lump excision should be recommended since FNAB is < 100 per cent sensitive for breast cancer[4] (although a positive result is 99 per cent specific) and the absence of a positive report on a suboptimal specimen should not be taken as reassurance. Further prospective studies are needed to assess the value of FNAB in apparently benign lumps diagnosed on less strict criteria, and on dominant lumps in dysplastic breasts. Surgeons considering a conservative policy towards benign breast lumps based on FNAB should carry out a prospective audit of their results since both biopsy technique and cytological assessment are operator dependent. It is possible that optimal results may only be obtained in specialist breast clinics seeing large numbers of such patients. Such a policy should include prolonged follow-up with repeat biopsy, since at present there is insufficient information on the sensitivity of FNAB in detecting these rare carcinomas in young women.

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Surgical workshop

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Microdochectomy: the precise identification of the suspicious duct

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Patients with nipple secretion without a palpable mass in the breast present diagnostic and therapeutic problems[1]. With regard to diagnosis some suggest that ductography is the most important investigation[2–5]. A number of differing techniques for microdochectomy have been described[6–8].

This study demonstrates a simple and quick method for carrying out a precise microdochectomy if a catheter is placed into the secretory duct.

Patients and methods

Between October 1987 and December 1989 microdochectomy was carried out in 35 patients with single-duct spontaneous nipple discharge, serous or haemorrhagic in colour, with no mass in the breast on clinical examination and mammography. In all cases cytological examination of the secretion and ductography were carried out. Those patients with abnormal nipple discharge and a breast tumour detected by clinical examination or mammography were excluded.

The technique for carrying out microdochectomy consists of three stages:

1. *Insertion of the catheter into the secreting duct.* A 22-gauge Abbocath (Abbot, Sligo, Ireland) 32 mm long, or a 24-gauge Abbocath, 19 mm long, is introduced into the suspicious duct using the technique for galactography[9]. This procedure can be carried out a few hours before the surgical intervention and the catheter kept in place by means of sticking plaster.
2. *Circumareolar incision.* With the patient under general or local anaesthesia, an incision is made at the edge of the areola extending around approximately one-third of the circumference. The centre of the incision is at the point of intersection with the radius on which the suspicious duct is located. This is determined from the information provided by the ductogram using craniocaudal and mediolateral

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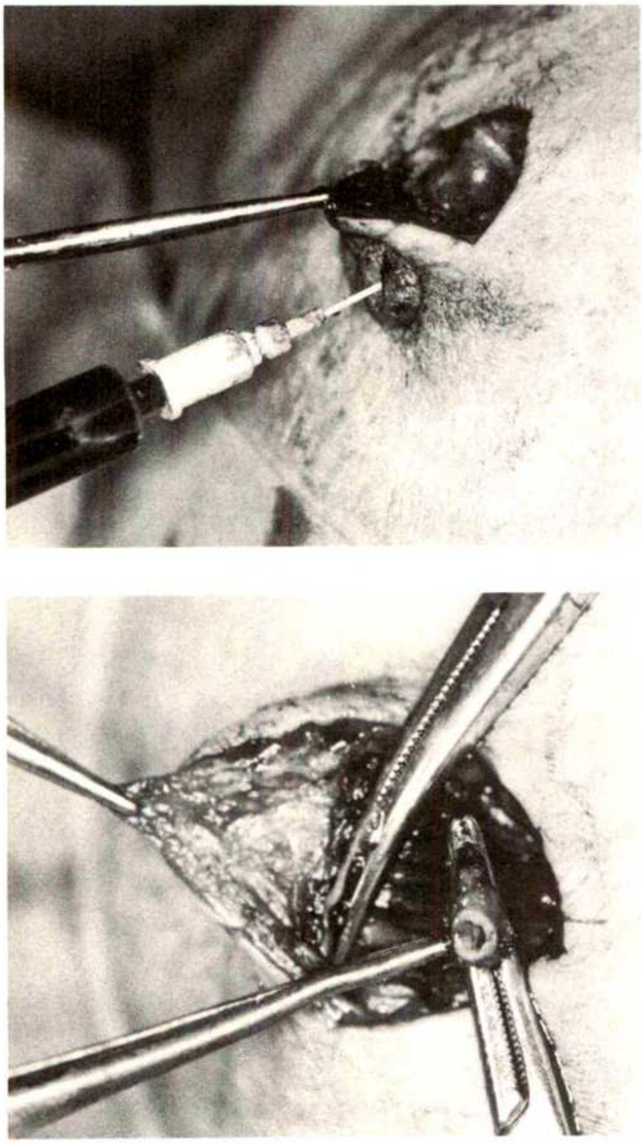

Figure 1 *Phases of microdochectomy:* **a** *the circumareolar incision and the injection of methylene blue into the secretory duct,* **b** *identification of the suspicious duct and section of the duct near to the base of the nipple*

projections. These details are most important in determining the area of the lesion to be removed.

3. *Identification of the suspicious duct.* The catheter needle is introduced into the catheter within the duct gently and only partially to avoid perforation of the duct with the tip of the needle. Moving the catheter inside the duct the stiff needle is detected by fingertip, through the circumareolar incision, locating the suspicious duct. The needle is withdrawn from inside the catheter and a small quantity of methylene blue (0·2–1 ml) injected (*Figure 1a*), and a visual check is made as the duct fills with dye. With careful dissection as far as the base of the nipple and good haemostasis, the suspicious duct is easily isolated. The duct is sectioned at its distal extremity (*Figure 1b*) and then dissected along its entire length and removed with a small cone of breast tissue surrounding the duct.

The time taken for carrying out microdochectomy was about 30 min in most cases.

The histological findings revealed duct ectasia in nine cases, fibrocystic disease in 13 cases, papilloma in nine cases and papillomatosis in one case, and in three patients the diagnosis was of intraductal carcinoma, with one of the three cases presenting foci of microinvasion. The patients with a diagnosis of intraductal carcinoma received further surgery. No nodal metastases were found.

Discussion

The management of patients with single-duct nipple discharge continues to be a subject for discussion[7].

Some advocate intraductal injection of methylene blue for the identification of the suspicious duct before surgery[10,11]. A recent study[8] describes the advantages of the injection of methylene blue through a 30-gauge 'anterior chamber' needle for the identification of the duct responsible for the discharge. In our study, the localization of the suspicious duct was carried out with the aid of an Abbocath, with needle, inserted inside the duct. The technique allows the injection of methylene blue during the surgical intervention, avoiding extravasation of dye and verifying the diseased duct.

Ductography is carried out routinely as it is a simple, rapid examination and of great help in verifying the topography of the duct and the site of the lesion. In two patients nipple discharge ceased after ductography and in these cases the ductograms were fundamental for determining the biopsy site.

Currently we carry out microdochectomy under local anaesthesia, having identified the suspicious duct by using the Abbocath needle only. This procedure is simple, accurate and rapid. We emphasize the importance of close collaboration between surgeon, radiologist and pathologist for the successful management of patients with abnormal nipple discharge.

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Meakin adjuvant regimen in premenopausal patients with breast cancer

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A 10-year experience using ovarian ablation and prednisolone as adjuvant therapy for premenopausal patients with breast carcinoma, emphasizing tolerability and morbidity is reported. Thirty patients (15 aged <45 years, 15 aged $\geqslant 45$ years; range 28–54 years) underwent mastectomy/lumpectomy with axillary clearance (with or without local irradiation) followed by ovarian irradiation and prednisolone therapy (2·5 mg three times daily for 5 years). Patients were reviewed every 3 months for the first 3 years and every 6 months thereafter. Follow-up was between 1·5 and 10 years (median 5 years). Twenty-four patients are still alive. Three patients stopped therapy because of side-effects. There was a mean(s.e.m.) weight gain of 8·46(1·69) per cent on therapy. Nineteen patients have been weaned off prednisolone over a period of 0·5–7·5 months (median 2 months) and the median length of time off steroids is now 3 years (range 0·5–5 years). This regimen appears to be associated with an acceptable level of patient tolerability and a low chronic morbidity rate and should be considered as an alternative to adjuvant systemic cytotoxic therapy.

Keywords: Adjuvant therapy, premenopausal breast carcinoma

The type of adjuvant therapy to be used in premenopausal women with breast cancer remains controversial. Many clinicians are sceptical of the use of adjuvant systemic combination cytotoxic chemotherapy because of toxicity and because of evidence suggesting that cytotoxics act by a 'castration effect'[1,2]. In 1979, Meakin *et al.* demonstrated a statistically significant delay in recurrence in premenopausal patients aged 45 years or more, using ovarian ablation by irradiation and prednisolone (7·5 mg per day for up to 5 years)[3]. We have used this regimen in the Tayside region and have included patients aged under 45 years. In this report we emphasize patient acceptability, compliance and morbidity.

Patients and methods

A retrospective study was carried out of 30 premenopausal patients with node-positive breast carcinoma, treated using the Meakin regimen over the past 10 years Ages at presentation ranged from 28 to 54 years (median 45 years) and 15 patients were aged 45 years or less. They underwent either mastectomy/axillary clearance ($n=20$) or lumpectomy/axillary clearance with or without local irradiation ($n=9$), and one patient underwent lumpectomy and local irradiation for a medially sited primary tumour. Surgery was followed by ovarian irradiation of 1500 cGy at 4 meV in five fractions over 5 days and oral prednisolone therapy The typical dose of prednisolone was 2 5 mg three times daily, continued for an average of 5 years Patients were followed at the outpatient clinic every 3 months for the first 3 years and every 6 months thereafter. At each outpatient clinic visit, routine urinalysis, weight and blood pressure were recorded and documented. Any patient with bone pain was investigated with plain radiography and a bone scan was performed to exclude metastatic deposits; concurrently a radiological assessment was made to exclude osteoporosis as a cause of the bone pain.

The total group treated over the 10-year period has been considered as two subgroups· patients in group A were aged less than 45 years and those in group B were aged 45 years or over The side-effects of the steroids and tolerance of the regimen have been compared.

Results

Group A

Fifteen patients with an age range of 28–44 years (median 40 years) have been followed for 2–10 years (median 6 years). The mean(s.e.m.) distant disease-free survival rate was 5·2(0·85) years. Three group A patients have died as a direct result of their disease.

Steroid therapy. The usual dose of prednisolone was 2·5 mg three times daily. One patient was given 2·5 mg twice daily and one who suffered from rheumatoid arthritis was given 5 mg twice daily, which in addition alleviated her arthritis symptoms. The duration of therapy was 5 years, although one patient required to be changed to tamoxifen after 9 months because it was felt that she was escaping from her initial adjuvant therapy (metastatic nodes in her neck were increasing in size). Cushingoid facies was the only side-effect seen and this required therapy to be stopped in two patients, one at 5 months, and one at 1 year (*Table 1*). There was no evidence of hypertension, diabetes mellitus, dyspepsia, or symptomatic osteoporosis.

There was a mean(s e.m.) weight gain of 8·4(2·96) per cent on steroid therapy. Of the group A patients weaned off therapy so far ($n=11$), the median period of weaning was 2 months (range 0·5–7·5 months). One patient was required to restart therapy after a weaning period of 1 month because of tiredness and lassitude. She was recommenced at a dose of 4 mg and was successfully reduced at a rate of 1 mg/month.

Group B

Fifteen patients (age range 45–54 years, median 47 years) have been followed for a period of 2–9 years (median 5 years) The mean(s.e.m.) distant disease-free survival rate was 5(0·77) years. Three group B patients have died as a direct result of their disease

Steroid therapy The usual dose was again 2·5 mg three times daily over a period of 5 years. One patient was given 2·5 mg

Table 1 *Side-effects of prednisolone requiring cessation of therapy*

	Cushingoid facies	Hypertension	Depression
Group A ($n=15$)	2	0	0
Group B ($n=15$)	1	1	1

0007–1323/90/111219–02

twice daily and one was given 5 mg twice daily. One patient developed side-effects of raised blood pressure, Cushingoid facies and endogenous depression (*Table 1*). Her symptoms resolved on cessation of therapy. There was no other overt evidence of steroid related side-effects. There was a mean(s.e.m.) weight gain of 8·5(1·7) per cent on therapy. Of the patients in group B weaned so far ($n = 8$), the median period of weaning was 3 months (range 2–6 months). One patient was required to restart therapy after a weaning period of 4 months because of myalgia. She was recommenced at a dose of 2 mg and was successfully reduced at a rate of 0·5 mg/month.

In total, from both groups, 19 patients have been successfully weaned off steroid therapy. The median length of time off steroids is now 3 years (range 0·5–5 years). Of the six patients who have died, three died after cessation of steroids, although two of these had their steroid therapy course stopped prematurely after less than 1 year (one due to neck nodes and one due to side-effects). All of these patients died as a direct result of metastatic disease, and there was no apparent 'Addisonian' contribution to the cause of death.

Discussion

Although the use of adjuvant systemic chemotherapy in premenopausal patients with early breast cancer appears to improve survival[4,5], its mechanism of action remains controversial. It may act by a castration effect[1,2], a hypothesis that is supported by the strong association between the improved survival rates using the cyclophosphamide, methotrexate, fluorouracil regimen and the progesterone receptor-positive status of the tumour and the induction of amenorrhoea[6]. While the survival rates may be improved the toxicity of this regimen remains a problem and in this group of patients with a poor prognosis, preservation of a more normal quality of life would be highly desirable. In a study at the Royal Marsden Hospital[7] 79 per cent of patients receiving adjuvant chemotherapy admitted to very unpleasant side-effects, including nausea, vomiting, malaise and alopecia, and 30 per cent said that they would 'never undergo the treatment again'. Other reports have shown an increased incidence of psychiatric morbidity, which can extend to at least 6 months after completion of a combination chemotherapy course[8,9]. The endocrine effect of chemotherapy may be more readily achieved by direct ovarian ablation. The use of adjuvant tamoxifen would be the best option in terms of toxicity, but despite being the subject of multicentre trials, a statistically significant effect on the mortality rate has not yet been shown in patients aged less than 50 years, partly because of sample size limitations and partly because tamoxifen has frequently been used in combination with chemotherapy[4].

In 1964, Nissen-Meyer reported delayed recurrence rates in premenopausal patients with stage II breast carcinoma, using either surgical oophorectomy or ovarian irradiation together with 10 mg prednisolone for 3–4 years[10]. In 1979, Meakin *et al.* studied a population of 705 patients who had undergone mastectomy and local irradiation for breast carcinoma[3]. In the premenopausal group, patients receiving ovarian ablation alone had delayed recurrence and prolonged survival, but this did not achieve statistical significance. The addition of prednisolone therapy achieved significant levels in the delay of recurrence ($P = 0{\cdot}04$) and prolonged survival ($P = 0{\cdot}02$). For these reasons we have used this regimen in the Tayside region in many premenopausal patients with node-positive breast carcinoma.

Our overall results of a mean(s.e.m.) distant disease-free survival rate of 5·1(0·57) years and an overall survival rate of 5·5(0·52) years compare favourably with the results from the original trial of Meakin *et al*, although our cohort is too small for any statistical comparison. The incidence of side-effects appears to be appreciably smaller than with the use of chemotherapeutic agents. The main side-effects in our patients ($n = 3$) were Cushingoid facies and weight gain. No serious side-effects of prednisolone therapy were seen within the period of follow-up (1·5–10 years) but this period is probably too short for any long-term sequelae of steroid therapy. Any long-term side-effects must be viewed in perspective with the poor prognosis generally expected of this group of patients. There appears to be no discernible difference in morbidity in the patients in groups A and B, and we feel that to deny patients in group A treatment using this regimen because of possible long-term steroid side-effects is unnecessarily cautious.

In weaning patients off steroids, two patients showed signs of steroid withdrawal (lassitude, tiredness and myalgia) and they required weaning over a long period. Both of these patients have now been successfully weaned. In the light of these problems, we have developed a standard policy of weaning the patients off steroids at a rate of 1 mg/month. This policy appears satisfactory and no patient has since shown withdrawal signs.

We have shown that this regimen can be easily managed by the attendant clinicians with a policy of a standard dosage (2·5 mg three times daily), set follow-up intervals and a set weaning period. The regimen appears to be well tolerated by patients. Any adjuvant therapy that confers benefit to the patient but does not suffer from the degree of toxicity of systemic combination chemotherapy warrants further evaluation in wider use in premenopausal patients of all ages.

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Reduced psychological morbidity after breast conservation

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Psychological morbidity was compared in 52 patients treated by mastectomy and 67 patients treated by lumpectomy for early breast cancer. An informal counselling service was provided for all patients. Morbidity was measured at 6, 9 and 12 months after surgery with two self-rating scales: the general health questionnaire and the Leeds depression and anxiety scales. There was a significant excess of severe depression in the mastectomy group. In contrast to the findings of previous research, this result suggests that breast conservation reduces psychological morbidity.

Keywords: Breast neoplasms, conservation surgery, depression, anxiety

Psychological morbidity after mastectomy is well recognized[1,2]. To what extent it stems from knowledge of cancer or from loss of the breast has long been the subject of debate[1–4]. Psychological morbidity might be reduced if the breast were conserved but studies on the effects of lumpectomy, while showing that it helps body image problems, have so far failed to confirm that it reduces depression or anxiety[5–9].

A change in policy at the Royal Infirmary in Glasgow from mastectomy to lumpectomy allowed the psychological morbidity associated with the two operations to be compared.

Patients and methods

Consecutive patients under the age of 80 years with stage I or II breast cancer were eligible for the study An initial block of 57 patients was treated by simple mastectomy and axillary sampling A subsequent block of 74 patients was treated by lumpectomy whenever possible. All patients received informal counselling from a nursing sister at each outpatient visit.

Psychological morbidity was measured with two self-rating scales the general health questionnaire and the Leeds general scales for the self-assessment of depression and anxiety[10,11] The general health questionnaire consists of 60 items which measure non-specific psychological morbidity Scores range from zero to 60. The questionnaire contains somatic and social items which might be endorsed by patients with purely physical problems Two of its subscales consist almost entirely of psychic items (anxiety/insomnia and severe depression) and were analysed separately Scores on each subscale range from zero to 21 Each Leeds scale has six items, scores for both depression and anxiety range from zero to 18 The patients completed these scales in the outpatient department at 6, 9 and 12 months after surgery.

Statistical analysis

Because the questionnaire scores often showed marked positive skew, non-parametric methods were used Differences within each treatment group over time were analysed by Friedman analysis of variance. Differences between the two groups were analysed by two-tailed Mann–Whitney *U* tests

Results

Of 57 patients undergoing mastectomy, four were unwilling to take part and one who could not read was excluded. After the change in surgical policy, four patients had lesions unsuitable for lumpectomy and were left out of the study Of 70 patients treated by lumpectomy, three were excluded (two moved house and one refused) Subsequently, in the 119 patients entering the study, several interviews were missed In the mastectomy group, two interviews were missed because a patient died and three through patient default In the lumpectomy group, one was missing because a patient died, four because patients left the clinic and 12 because patients defaulted

From all causes there were 22 missing interviews (6 per cent of a potential 357). For each patient with missing data, the means of the scores that she obtained on the questionnaires at other times were substituted for the missing scores.

Table 1 shows the demographic and other background data for the 119 patients included in the analyses. Data for the two groups were similar. Follow-up treatment was similar, except that patients in the lumpectomy group received 6 weeks of radiotherapy compared with only 3 weeks in the mastectomy group.

Results for the self-rating scales are shown in *Table 2*. At each assessment there was a trend on virtually all scales towards higher morbidity in the mastectomy group compared with the lumpectomy group. Friedman analyses of variance showed that none of the scores in each treatment group varied significantly over time. The mean scores over time in each group were compared by Mann–Whitney *U* tests (*Table 3*). On the severe depression subscale of the general health questionnaire, the mastectomy group scored significantly higher than the lumpectomy group ($P < 0{\cdot}03$) A similar, non-significant, trend was seen on the Leeds depression scale and on the two measures of anxiety. The difference on the anxiety/insomnia scale approached significance ($P < 0{\cdot}08$).

Table 1 *Demographic data*

	Mastectomy ($n=52$)	Lumpectomy ($n=67$)
Age (years)		
Mean(s d)	56(12)	56(12)
Range	33–78	31–78
Marital status		
Married	38 (73)	45 (67)
Widowed	9 (17)	13 (19)
Divorced	3 (6)	2 (3)
Never married	2 (4)	7 (10)
Further education		
None	49 (94)	58 (87)
College	3 (6)	9 (13)
Past psychiatric treatment		
None	35 (67)	46 (69)
General practitioner	17 (33)	20 (30)
Psychiatrist	0	1 (2)
Postoperative treatment		
Radiotherapy alone	10 (19)	10 (15)
Tamoxifen alone	13 (25)	17 (25)
Both	13 (25)	12 (18)
Neither	16 (31)	28 (42)

Values in parentheses are percentages unless otherwise stated

Table 2 *Comparisons between mastectomy* (n = 52) *and lumpectomy* (n = 67) *groups*

	Time after surgery					
	6 months		9 months		12 months	
Scale	Mastectomy	Lumpectomy	Mastectomy	Lumpectomy	Mastectomy	Lumpectomy
General health questionnaire	3 (0–9)	1 (0–5)	1 5 (0–9)	1 (0–5)	1 (0–7)	1 (0–7)
Anxiety/insomnia subscale	3 5 (1–9)	3 (1–6)	4 (2–8)	3 (1–7)	4·5 (1–7)	3 (1–6)
Severe depression subscale	0 (0–2)	0 (0–1)	0 (0–2)	0 (0–0)	0·5 (0–2)	0 (0–1)
Leeds depression	3 (1–5)	2 (1–5)	3 (1–6)	2 (0–4)	3 (1–6)	2 (0–5)
Leeds anxiety	4 (1–9)	2 (0–7)	3 5 (0–7)	3 (0–6)	4 5 (0–8)	2 (0–6)

Values are median scores with interquartile ranges in parentheses

Table 3 *Comparisons of mean scores over time in mastectomy* (n = 52) *and lumpectomy* (n = 67) *groups*

Scale	Mastectomy	Lumpectomy
General health questionnaire	2 (1–9)	1·3 (0–8)
Anxiety/insomnia subscale	3 5 (2–8)†	3 (1–6)
Severe depression subscale	0 7 (0–2)*	0 (0–1)
Leeds depression	3 (1–5)	2·3 (1–5)
Leeds anxiety	3 3 (1–8)	2 3 (1–6)

* $P<0$ 03; † $P<0{\cdot}08$ (Mann–Whitney U tests). Values are medians of average scores over time, with interquartile ranges in parentheses

Discussion

A scientific assessment of whether lumpectomy is less psychologically traumatic than mastectomy is difficult. Ideally, a very large, unselected sample of women would be allocated at random to either operation and prospectively assessed using methods free from possible observer bias. In practice this ideal has not been achieved, partly because of ethical problems.

In the Cancer Research Campaign's randomized trial comparing the psychological effects of breast conservation and mastectomy, entry had to be restricted to those patients who had no strong preference for either operation[8]. Such an unavoidable selection bias might have reduced the chances of detecting differences. Furthermore, comparisons of psychological morbidity were based on a single assessment at a time varying from 4 to 32 months after surgery and differences in morbidity at different time intervals might have been masked. In that study there were no significant differences between groups in observer ratings of mood, although there was an unexpected trend towards higher morbidity in the lumpectomy group: 38 per cent of 48 lumpectomy patients were judged to have depression, anxiety or both compared with only 33 per cent of 53 mastectomy patients. The authors suggested that morbidity in their lumpectomy group might have been high because all these patients received radiotherapy and because some worried that treatment had been inadequate.

Two other randomized studies have been reported. From a sample of 65 women with early breast cancer, Schain and her colleagues studied 38 patients willing to be randomized to mastectomy or lumpectomy and radiotherapy[7]. A single assessment was made by postal questionnaire. The lumpectomy patients felt significantly less negative about their appearance when naked but there were no significant differences for mood. A more recent randomized study of 34 patients gave a very similar result. fewer body image problems in the lumpectomy group but no significant mood differences[9]. Selective entry to randomization and small sample sizes may have prevented differences from emerging in these reports.

Two small non-randomized studies showed that there were fewer body image problems but no significant mood differences in lumpectomy compared with mastectomy patients[5,6]. Here selection bias may have arisen because some patients chose their own operation or were omitted because of emotional distress.

In this study we made several prospective assessments but the patients were not randomized. This had the scientific advantage that patients did not choose their own operation and none was omitted for ethical reasons. The criticism may be levelled that our finding of more depression in the mastectomy group might be due to factors other than the change in surgical policy. Although fewer lumpectomy patients refused to take part, there were more missing data in that group subsequently; but overall the amount of missing data was small. The mastectomy group tended to be looked after by several consultant surgeons within different units. Because of retirements those treated by lumpectomy were usually cared for by surgeons within a single unit but all patients were counselled by the same nurse.

While we cannot be certain there were no confounding factors, the two patient groups were similar both demographically and in the proportions who received different types of follow-up treatment. The course of radiotherapy was longer in the lumpectomy group and there was a trend for those who received radiotherapy to have higher scores on the self-rating scales than those who did not (details available) There was no such trend in the mastectomy group, consistent with our previous report that after mastectomy emotional distress due to radiotherapy is usually short lived[13]. The more prolonged radiotherapy after lumpectomy possibly increases morbidity. Had all our lumpectomy patients received radiotherapy, as in the Cancer Research Campaign's study[8], differences between the lumpectomy and mastectomy groups might have been smaller.

Another difference betwen the Cancer Research Campaign's study and this one is that the former used both observer and self-rating scales. This is unlikely to account for the differing results In previous studies of mastectomy patients, we used the same self-rating scales and observer scales and both measures gave similar results[12–14]. In the Cancer Research Campaign's study, the self-rating scales showed the same trend as the observer scales. Self-rating scales avoid possible observer bias when the treatment is not blind.

These results are consistent with the belief that lumpectomy is less psychologically traumatic than mastectomy. Since it is generally agreed that there are fewer body image problems after lumpectomy[5–9], these results reinforce the view, reflected in recent changes in surgical practice[15], that women with breast cancer should be offered, if technically feasible, the option of conservation.

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Impaired polymorphonuclear leucocyte function in patients undergoing hepatectomy: adenylate energy charge and superoxide anion production in relation to hepatic mitochondrial redox state

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Patients undergoing hepatectomy have an increased susceptibility to infection. We therefore studied the energy metabolism of the polymorphonuclear leucocyte (PMN), focusing on energy charge and function, especially superoxide anion (O_2^-) generation, in relation to the hepatic mitochondrial redox state. By labelling the PMN adenine nucleotide pool with radioactive adenine and by superoxide dismutase-inhibitable reduction of ferricytochrome c, *the energy charge and O_2^- production was measured in 18 patients with hepatoma (non-cirrhotic, seven; cirrhotic, 11) undergoing hepatectomy. Their arterial ketone body ratios (KBRs), reflecting the hepatic mitochondrial redox potential, were above 0·7 before operation. After surgery, the 18 patients were divided into two groups: group A, $KBR > 0{\cdot}7$, $n = 10$; and group B, $KBR < 0{\cdot}7$, $n = 8$. The energy charge and O_2^- release in group B decreased significantly from preoperative values ($P < 0{\cdot}001$ and $P < 0{\cdot}01$ respectively) and when compared with group A ($P < 0{\cdot}05$ and $P < 0{\cdot}01$ respectively). These results suggest that impaired hepatic energy metabolism ($KBR < 0{\cdot}7$) in hepatectomized patients leads to impaired energy charge and O_2^- production in the PMNs.*

Keywords: Leucocyte, hepatectomy, adenylate energy charge, superoxide, ketone body ratio

Hepatic resection for hepatoma in cirrhotics often leads to 'hepatic' energy crisis' followed by impaired metabolic homoeostasis and multiple organ failure[1] Under these conditions the host defence system also becomes impaired, resulting in various kinds of infection and continued deterioration of hepatic energy metabolism. We have previously reported an inverse relationship between the mortality rate associated with multiple systemic organ failure and the arterial ketone body ratio (KBR. acetoacetate/3-hydroxybutyrate), which reflects hepatic mitochondrial redox potential (nicotinamide adenine dinucleotide (NAD^+)/NADH) (Reference 2).

The KBR is a reliable index of metabolic change in the liver[3–5] and is widely accepted as an assessment of hepatic function in various medical fields[6–8]. KBR is reported to be an early indicator of primary graft failure after liver transplantation[8–10].

To clarify the mechanism leading to increased susceptibility to infection in hepatectomized patients investigators have reported on the precipitating factors associated with the increased risk of sepsis in cirrhosis[11] or after hepatectomy[12] with special reference to reduction of the reticuloendothelial function in the liver. Little is known about postoperative granulocyte function, especially after hepatic resection. This study, therefore, examines the relationship between leucocytes and the liver by measuring the changes in adenylate energy charge and superoxide anion (O_2^-) release in polymorphonuclear leucocytes (PMNs) with respect to changes in the KBR

Patients and methods

Patients

To assess the effect of incubation time and cell concentration on the energy charge of PMNs, five healthy volunteers (three men and two women aged 21–36 years) and five histologically diagnosed cirrhotic patients (three men and two women aged 42–64 years) were studied

Eighteen patients (nine men and nine women aged 45–70 years) with hepatocellular carcinoma undergoing major hepatic resection were examined Eleven of these patients had cirrhosis KBR values of all 18 patients were above 0·7 before operation A KBR of more than 0·7 is normal, between 0·7 and 0·4 is indicative of subclinical hepatic failure, and below 0·4 is a sign of definite hepatic failure[2]. The 18 patients were divided into those with values of 0·7 or more (group A, $n = 10$) and those showing a decrease to below 0·7 for at least two consecutive days before the seventh day after operation (group B, $n = 8$) All patients in group B had cirrhosis Blood samples were taken for energy charge and O_2^- release of PMNs between the seventh and tenth days after operation

Preparation of human PMNs

PMNs were purified from heparinized blood (10 units/ml) using a previously described method[13]. They were isolated by Hypaque–Ficoll (Pharmacia, Piscataway, New Jersey, USA) density gradient centrifugation, followed by dextran sedimentation and hypotonic lysis of the erythrocytes The PMNs were then washed twice and suspended in Hank's balanced salt solution at a concentration of 1×10^7/ml. Viability measured by trypan blue exclusion was greater than 98 per cent

Methods of measurement of PMN energy charge

A 0·25 ml volume of the PMN-rich solution ($1–40 \times 10^3/\mu l$) was incubated with radioactive adenine ([^{14}C]adenine, 55 Ci/mol, Amersham International, Amersham, UK) at final concentrations of 2·3 μM for 10–120 min at 37°C The cells were washed twice in 5 ml cold Hank's solution (0–4°C) The radioactive metabolites of labelled PMNs were extracted by adding one-tenth volume of 7 N perchloric acid The supernatant was neutralized by an appropriate volume of 5 M potassium carbonate and extracts were chromatographed on silica gel plates (TLC-F254, E. Merck, Frankfurt, FRG) for 15 h at 4°C with isobutyl alcohol, amyl alcohol, ethoxyethanol, 25 per cent aqueous ammonia, and distilled water (15:10:30 15:25 volume/volume) together with 0·5 µmol adenosine triphosphate (ATP), adenosine diphosphate (ADP), adenosine monophosphate (AMP), inosine monophosphate (IMP), inosine, hypoxanthine and adenine[14] Radioactivities of the metabolites were counted in a liquid scintillation spectrometer (Packard Tricarb Model 3385, Downersgrove, Illinois, USA) at 80 per cent efficiency. The adenylate energy charge was calculated according to the formula proposed by Atkinson[15] as (ATP+1/2ADP)/(ATP+ADP+AMP), in which the concentration of each nucleotide was replaced by radioactivity.

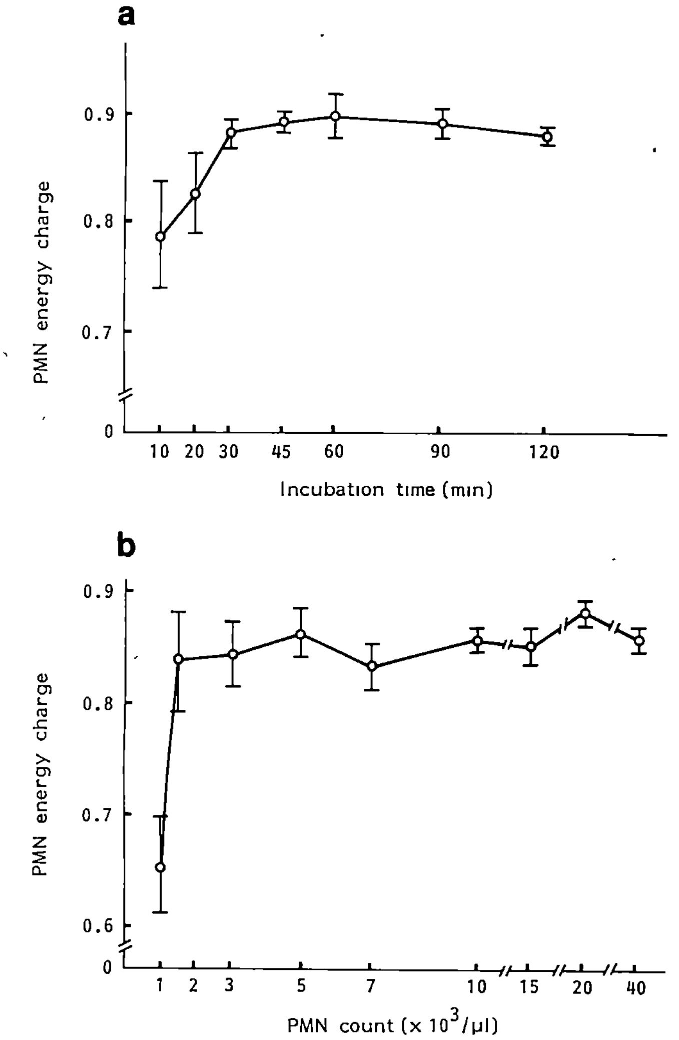

Figure 1 *Effect of incubation time at 37°C* **a** *and of polymorphonuclear leucocyte (PMN) count in PMN-rich solution* **b** *on PMN energy charge In* **a** *PMN counts in the solution were $20\times10^3/\mu l$ and in* **b** *incubation time was 30 min*

Assay of superoxide anion production by PMNs

Generation of O_2^- was determined by a spectrophotometer (UV-260, Shimadzu, Kyoto, Japan) after the superoxide dismutase-inhibitable reduction of ferricytochrome *c* (Sigma, St Louis, Missouri, USA) following stimulation with 1 mg/ml opsonized zymosan and 50 ng/ml phorbol myristate acetate at 37°C for 15 min[16].

Assays of acetoacetate and 3-hydroxybutyrate

To determine the KBR, acetoacetate and 3-hydroxybutyrate were measured enzymatically by methods previously reported[17,18] The enzyme used was obtained from Sanwa Chemical Co. Ltd., Nagoya, Japan

Statistical analysis

Results are expressed as mean(s.e.m.) and statistical analysis was calculated using Student's *t* test. *P* values of less than 0·05 were regarded as significant.

Results

In the five normal subjects, PMN energy charge measured by radiolabelled metabolites from [^{14}C]adenine gave the stable value of 0·88 after 30 min of incubation. Almost the same value was observed at PMN counts over $2\times10^3/\mu l$ (*Figure 1*). The control value of 0·88 was obtained at a PMN count of more than $10^4/\mu l$. Similar data were obtained in five cirrhotic patients (data not shown). We therefore measured the energy charge of PMNs in patients with PMN counts of more than $10^4/\mu l$ after incubation for 30 min.

Table 1 shows the perioperative changes in PMN counts and subpopulations in peripheral blood of 18 patients with hepatoma PMN numbers, as well as stab form neutrophils, in groups A and B increased significantly ($P<0·05$) when compared with the preoperative state. No significant differences in PMN numbers and their subpopulations were observed between groups A and B.

Table 2 shows the preoperative data concerning PMN counts, energy charge, and O_2^- release in the 18 patients. PMN counts in the peripheral blood were almost the same as in the seven non-cirrhotics and 11 cirrhotics. No significant difference was observed in the energy charge, or in the percentage radioactivity of ATP, ADP, AMP and hypoxanthine between the two groups. Moreover, no significant difference was observed in O_2^- release after stimulation with opsonized zymosan or phorbol myristate acetate between these two groups.

After operation, however, PMN energy charges in group B decreased significantly when compared with group A ($P<0·05$) and when compared with the preoperative state ($P<0·001$) (*Figure 2*). Moreover, the amount of O_2^- generated by PMNs in group B was significantly lower than in group A ($P<0·01$) and than in the preoperative state ($P<0·01$) when PMNs were stimulated by opsonized zymosan or phorbol myristate acetate (*Figure 3*).

All patients in group A and six patients in group B had an uneventful postoperative course The other two patients in

Table 1 *Perioperative changes in polymorphonuclear leucocyte counts in peripheral blood*

	Before operation	After operation	
	($n=18$)	Group A (KBR > 0·7, $n=10$)	Group B (KBR < 0·7, $n=8$)
Polymorphonuclear leucocyte counts ($\times10^3/\mu l$)	2·57(0·43)	4·61(1·15)*	4·56(0·43)*
Subpopulation ($\times10^3/\mu l$)			
Stab	0·12(0·09)	1·33(0·26)*	2·54(0·96)*
Segment	2·21(0·43)	3·42(1·85)	3·31(1·24)
Eosinophil	0·14(0·01)	0·12(0·03)	0·09(0·01)
Basophil	0·04(0·01)	0·03(0·01)	0·03(0·01)

Values are mean(s.e.m.), KBR, ketone body ratio, * $P<0·05$ compared with state before operation group B had further decreases in KBR to below 0·4 in parallel with a concomitant decrease in PMN energy charge and O_2^- release due to sepsis and hepatic failure, resulting in death on days 52 and 189 after operation.

Discussion

Despite technical and therapeutic advances in the management of surgical patients, infection remains a major cause of postoperative morbidity and mortality. There have been many investigations into PMN function after surgery in relation to chemotaxis[19,20], phagocytosis[20,21], respiratory burst[22] and O_2^- production[23]. El-Maallem and Fletcher reported that PMN microbicidal ability was markedly impaired, but phagocytosis was unaffected within 2 h of elective abdominal hysterectomy[21]. Bowers *et al.* reported impaired chemotaxis and adherence but found unaffected bacterial killing and phagocytosis in healthy kidney donors[20]. Some reports have emphasized the importance of serum factors[24], catecholamines[25], glucocorticoids[26] and increased number of immature forms of PMNs[21]. There is no information on possible mechanisms of deteriorating neutrophil

Table 2 *Preoperative data on counts, adenine nucleotide metabolism, and superoxide anion release by polymorphonuclear leucocytes in patients with hepatoma*

	Non-cirrhotics (n=7)	Cirrhotics (n=11)
PMN counts in venous blood (10^3/μl)	2·6(0·4)	2·3(0·3)
Percentage radioactivity		
Adenosine triphosphate	69·2(5·4)	63·8(8·2)
Adenosine diphosphate	13·1(2·5)	15·9(1·2)
Adenosine monophosphate	8·5(2·9)	4·7(1·3)
Hypoxanthine	6·4(3·6)	8·9(5·1)
PMN energy charge	0·872(0·15)	0·868(0·012)
PMN superoxide release (nmol/5 × 10^5 cells per ml)		
Opsonized zymosan (1 mg/ml)	18·7(2·5)	16·8(2·8)
Phorbol myristate acetate (50 ng/ml)	41·3(3·8)	44·1(5·2)

Values are mean(s.e.m.), PMN, polymorphonuclear leucocyte

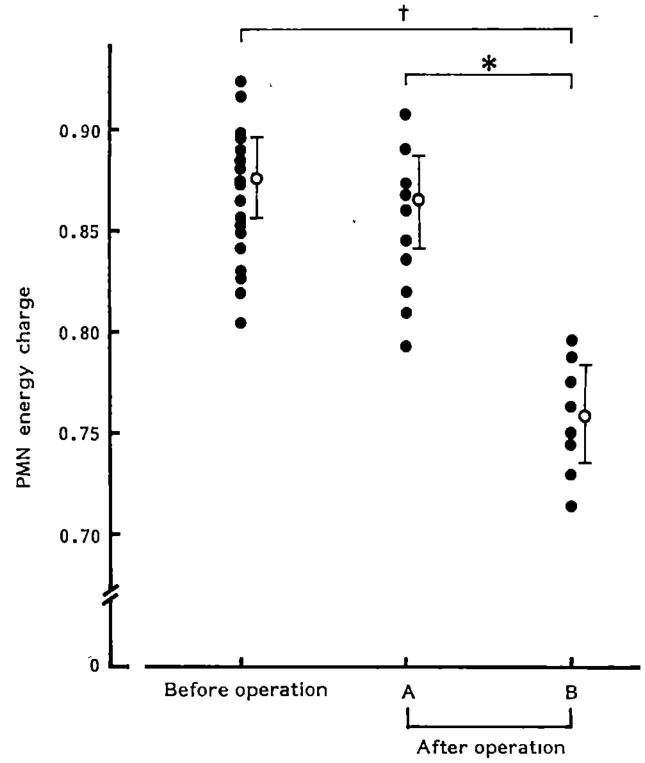

Figure 2 *Changes in the energy charge of polymorphonuclear leucocytes after hepatectomy. Patients were divided into two groups after operation according to the ketone body ratio (KBR). those with KBR values above 0·7 were classified as group A and below 0·7 as group B.* *P<0·05 *compared with group A;* † P<0·001 *compared with state before operation*

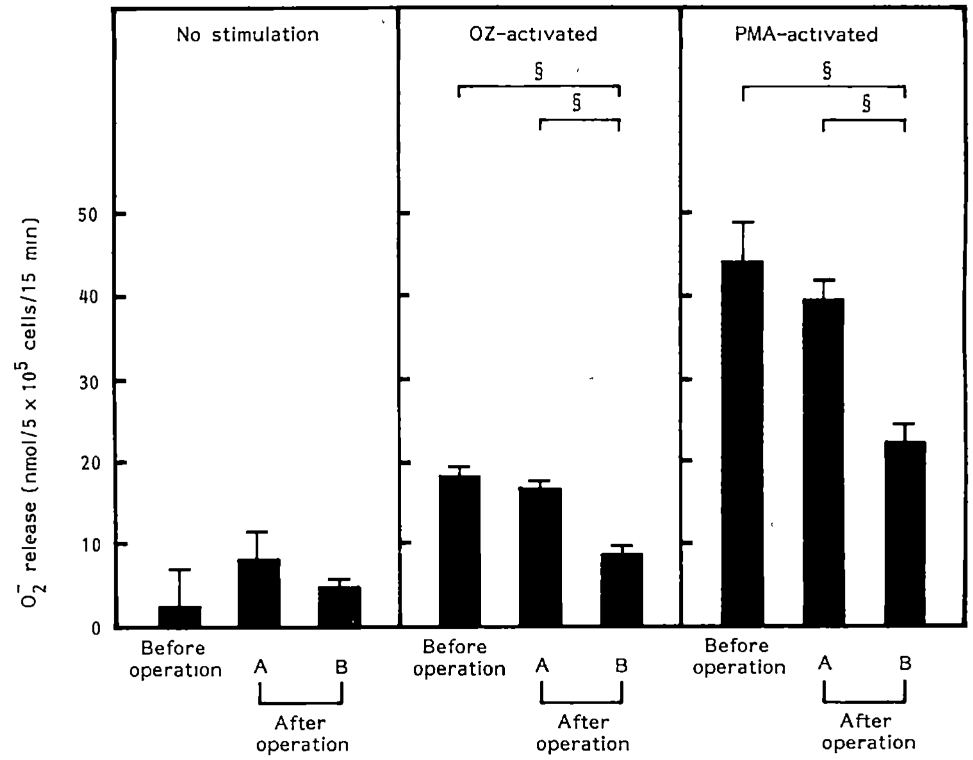

Figure 3 *Changes in superoxide production by polymorphonuclear leucocytes after hepatectomy A and B represent group A and group B, respectively, and their composition is described in the legend to* Figure 2 *O_2^-, superoxide anion, OZ, opsonized zymosan, PMA, phorbol myristate acetate,* §P<0·01

function after surgery, especially the energy status of the granulocyte itself.

We measured the adenylate energy charge of PMNs by labelling the PMN adenine nucleotide pool[14,27] for the following reasons. (1) incubation with adenine results in greater vitality than when PMNs are prepared alone because preparation takes at least 3 h, and (2) this method measures the distribution of adenine metabolites in PMNs, especially AMP, IMP, and hypoxanthine at lower cell counts than high performance liquid chromatography. Using this method, reliable energy charge values were obtained from normal healthy volunteers and cirrhotic patients. The mean(s.e.m.) values were 0·88(0·01) and 0·88(0·02) respectively. The normal value of about 0·88 is consistent with a previous report[27].

Preoperative data concerning PMN energy charge from patients with hepatoma showed similar values between non-cirrhotics and cirrhotics. The identity of the percentage radioactivities of [^{14}C]adenine metabolites between these two groups indicated that their PMN energy metabolism was the same although there was a tendency to see lower ATP and higher hypoxanthine levels in the cirrhotic group. If energy metabolism is slightly impaired, distribution of adenine metabolites will change (see our previous report on adenine nucleotide metabolism of platelets in human liver cirrhosis[14]). This is because adenylate deaminase, which catalyses the conversion of AMP to IMP, will be activated to maintain the energy charge due to an increase in ATP utilization and accumulation of AMP[28].

Data from the seventh to tenth days after operation were used to exclude the possible effects of anaesthetic agents, catecholamines, and blood transfusions on granulocyte function. The patients were divided into two groups according to the KBR as the best index in the classification of critically ill patients after hepatectomy, since postoperative KBR is thought to reflect the total results of preoperative, intraoperative and postoperative factors[2,29,30]. This study demonstrated that PMN energy charge significantly decreased when the KBR was less than 0·7. This decreased PMN energy charge in group B (KBR $<$ 0·7) is not considered to be due solely to increased numbers of immature forms of PMNs. If the postoperative change in immature neutrophil proportions was the cause, the decrease in PMN energy charge would be seen in group B or group A. No significant differences in PMN subpopulations were observed, however, between these two groups (*Table 1*). The critical value of 0·7 is in agreement with our previous studies[2,29]. Impaired hepatic energy metabolism associated with decreasing KBR gave rise to metabolic changes in the whole body, which include an accumulation of lactate and amino acids[2,31], enhanced protein catabolism[30] and increased serum osmolality[7]. Energy-deficient hepatocytes are unable to provide other organs with sufficient energy substrates to sustain vital functions[2] and such metabolic abnormalities may subsequently influence PMN energy metabolism. Impaired hepatic energy metabolism may be connected with impaired PMN energy status. We call this phenomenon the 'deterioration of the internal milieu surrounding the cells'.

Among PMN functions O_2^- production was studied because: (1) it has a crucial role in microbicidal activity; (2) its impairment leads to recurrent infections[32]; and (3) its production rate parallels cellular ATP levels and lactate production, indicating that the ability to produce O_2^- is energy dependent[33]. In addition, we measured O_2^- release in cases of no stimulation, opsonized zymosan activation and phorbol myristate acetate activation to compare the O_2^- production ability with this particular receptor-mediated reaction. Our data demonstrate that a decrease in O_2^- generation was the same for both opsonized zymosan-activated and phorbol myristate acetate-activated reactions, suggesting that O_2^- production ability by PMN is impaired after operation when the KBR is less than 0·7. This result duplicates the PMN energy charge findings.

Utoh *et al.* reported the impairment of O_2^- production after major surgery[23] but their results were, to some extent, inconsistent with ours. When the KBR was above 0·7, PMN O_2^- production was almost identical to preoperative values, despite major hepatic resection. Only when the KBR was below 0·7 did we observe impaired O_2^- generation, although the extent of impairment was similar. This may mean that most of the patients of Utoh *et al.* would be entered in our group B (KBR $<$ 0·7). The fluctuations of O_2^- production by PMN after surgery may be attributed to the various kinds of operation, the underlying pathology and postoperative managements. In these different states, it would be difficult for us to estimate PMN functions accurately in the absence of data about the KBR.

In conclusion, the energy charge as well as O_2^- release by PMN decreased significantly when the KBR was less than 0·7 after hepatectomy The increased susceptibility to infection due to impaired hepatic mitochondrial redox state is possibly explained, in part, by reduced PMN energy metabolism, leading to impaired PMN function.

Acknowledgements

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Development and reversibility of T lymphocyte dysfunction in experimental obstructive jaundice

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This study evaluates the effect of experimental biliary obstruction by bile duct ligation (BDL) and biliary drainage on cell-mediated immunity in Wistar rats. Immune status has been assessed by a mitogen stimulation test of T lymphocytes with phytohaemagglutinin. Animals were followed for up to 35 days after BDL. Regression analysis showed a significant negative correlation between lymphocyte function and the period of jaundice (correlation coefficient −0·57, $P<0{\cdot}001$*). Following BDL for 21 days, groups of animals had internal biliary drainage for 7, 14 and 28 days, and external drainage for 14 days. Compared with obstructed animals, 14 days internal drainage was required to improve lymphocyte function* ($P<0{\cdot}05$)*. Animals which had 14 days of external drainage had significantly lower lymphocyte stimulation than internal drainage animals* ($P<0{\cdot}05$)*. The results demonstrate that obstructive jaundice produces a progressive reduction of T lymphocyte function. This can be reversed by biliary drainage, internal drainage being more effective than external drainage.*

Keywords: Obstructive jaundice, cell-mediated immunity, internal biliary drainage, external biliary drainage

It has been demonstrated in clinical studies that patients with obstructive jaundice have a high incidence of infective complications following both therapeutic and diagnostic intervention[1–3]. Preoperative external biliary drainage has been developed in an attempt to reduce these and other complications[4] although clinical trials have failed to demonstrate any substantial benefit[5,6]. The exact cause of this increased susceptibility to infection is unknown, but it has been suggested that it may be due to some impairment of immune function.

Experimental studies in animal models have been limited and have concentrated on reticuloendothelial function[7,8]. More recent studies have shown prolonged allograft survival in jaundiced animals, suggesting some dysfunction of cell-mediated immunity[9]. This has been supported by the demonstration of specific and non-specific cellular immune suppression in animals with experimental obstructive jaundice[10,11].

In this study we have evaluated T lymphocyte function in an experimental animal model of obstructive jaundice. The T lymphocyte is a receptor, mediator and effector cell in specific cell-mediated immunity. It therefore plays a crucial role in the elimination of bacterial infection. After a period of obstructive jaundice two further models were used to demonstrate if any immune suppression could be reversed by biliary drainage. The first simulates the human situation of either operative decompression or endoprosthesis insertion and the second reproduces preoperative external biliary drainage. The hypothesis tested is that, after a period of obstructive jaundice, internal biliary drainage restores immune competence more quickly than external biliary drainage.

Materials and methods

All the procedures were performed using adult female Wistar rats (230–320 g) under ether anaesthesia. The animals were housed in small social groups and fed standard rat chow and water as required. The study was carried out under the regulations of the United Kingdom Animals (Scientific Procedures) Act 1986. Animals were assigned to different groups as shown in *Table 1*. Control animals had no surgical procedure. Sham operated animals had a laparotomy and mobilization of the common bile duct. On killing, each animal had the spleen removed for lymphocyte testing, blood taken for liver function tests, and some had bile and cannulas sent for bacteriology.

Bile duct ligation (BDL)

This was performed through a 2 cm upper midline incision. The supraduodenal bile duct was identified and doubly ligated with 5/0 silk, below the confluence of the right and left hepatic ducts, and then divided.

Internal biliary drainage (ID)

This was performed by a technique similar to that described by Ryan *et al.*[12]. The dilated biliary system was drained with a 21 G needle after which a choledochoduodenostomy was fashioned over a silastic stent (Dow Corning, Michigan, USA, internal diameter 0·5 mm) using 6/0 silk. A silicone rubber cuff on the duodenal end of the stent prevented dislocation.

External biliary drainage (ED)

This model involved an adaptation of a choledochovesical fistula originally described by Diamond and Rowlands[13]. At the initial

Table 1 *Groups of experimental animals*

Group	No of animals
Control	10
Sham operated	10
Bile duct ligation (BDL)	
7 days	10
14 days	10
21 days	10
35 days	10
Internal drainage (after 21 days BDL)	
7 days	10
14 days	9
28 days	10
External drainage (after 21 days BDL)	
14 days	9

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operation the abdomen was opened via upper and lower midline incisions. The common bile duct and bladder were then mobilized and a silastic cannula (internal diameter 0·5 mm) was tied first into the bladder and then the divided bile duct. Dislocation of the cannula was prevented by a silicone rubber cuff at either end. Biliary obstruction was obtained by kinking and tying the tube near its upper end. When drainage was required, a second laparotomy was performed and this tie removed. The dilated biliary tree could then drain externally via the bladder.

In vitro *lymphocyte assay*

Rat splenic lymphocytes were tested by a proliferative response to a T cell mitogen[14]. The spleens were removed when the animals were killed with the assay beginning almost immediately. Splenic tissue was minced into a fine suspension in RPMI-1640 Culture Medium (Flow Laboratories Ltd., Rickmansworth, UK) and excess red cells removed with red blood cell lysing buffer. The lymphocytes were isolated by centrifugation on Ficol-Hypaque Density Medium (Pharmacia Ltd., Milton Keynes, UK) and washed three times before being resuspended in a culture medium of RPMI-1640, L-glutamine, penicillin, streptomycin and 10 per cent fetal calf serum at a cell concentration of 8×10^6 cells/ml in a microculture plate. The lymphocytes were then stimulated with 5 μg phytohaemagglutinin-M (Difco Laboratories Ltd., East Molesey, UK) at 37°C in 5 per cent CO_2 for 48 h. Blast transformation was labelled by 1 μCi [^{3}H]-thymidine in culture for a further 18 h. The cells were finally removed in a Titertek® Cell Harvester (Flow Laboratories Ltd.) and the filter discs immersed in 5 ml toluene scintillation fluid. The incorporation of [^{3}H]-thymidine was counted using the tritium window of an Ultrabeta 1210 Scintillation Counter (LKB Instruments Ltd., Croydon, UK). The results are expressed as the mean of a triplicate set.

Statistical analysis

The results from each group of animals were expressed as the mean scintillation count (95 per cent confidence limits). Relevant groups were compared by a two-sample Student's t test and regression analysis on a CP/M based statistical package (AMSTAT Consumer Electronics, Brentwood, UK). A significant difference was indicated by $P<0{\cdot}05$.

Results

Biochemistry

The effect of biliary obstruction on bilirubin levels can be seen in *Figure 1*. All the BDL groups showed great elevation of bilirubin with maximum levels after 7 days of 229(38) μmol/l. The effectiveness of the drainage models was seen as early as 7 days, the bilirubin level in the ID group falling to 4·8(1·6) μmol/l. After 14 days ED, animals had higher bilirubin levels than controls, 7·9(1·4) μmol/l *versus* 1·8(0·6) μmol/l respectively ($P<0{\cdot}05$); however there was no difference compared with animals 14 days after ID, 4·2(1·7) μmol/l, and these levels were within the normal range.

Bacteriology

None of the samples from the BDL animals grew any bacteria after 48 h. For ID animals 18 out of 20 cultured cannulas grew bacteria. Coliforms were the most frequently isolated organisms. ED animals had positive cannula cultures on two occasions out of nine. Both were coagulase negative *Staphylococcus*. Despite positive cultures none of the ID or ED animals were considered to have clinical evidence of infection.

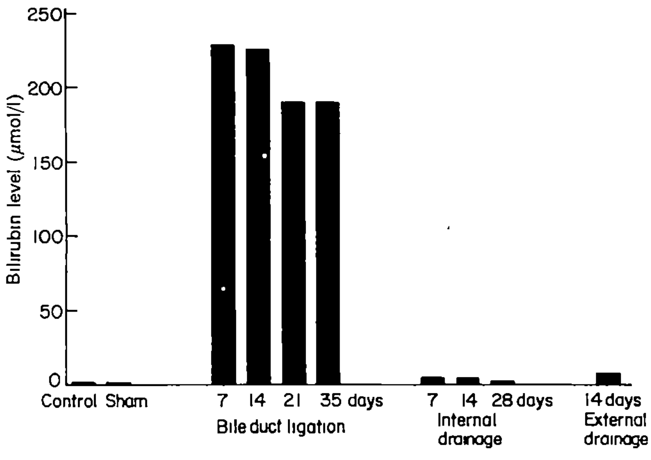

Figure 1 *Mean bilirubin levels in experimental biliary obstruction and drainage*

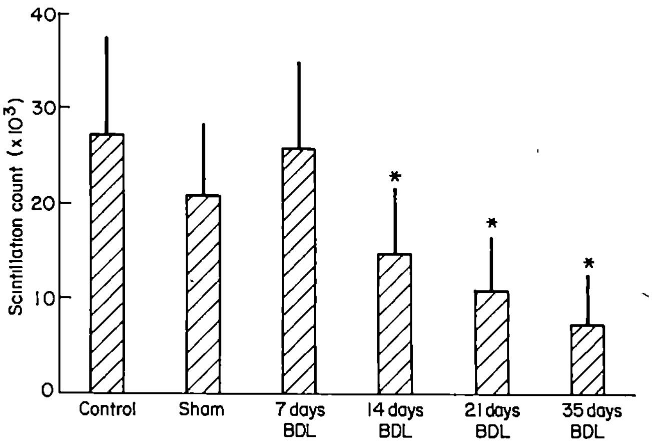

Figure 2 *Mean lymphocyte stimulation (scintillation count) in progressive obstructive jaundice. Bars show 95 per cent confidence limits* *P<0·05 *compared with controls. BDL, bile duct ligation*

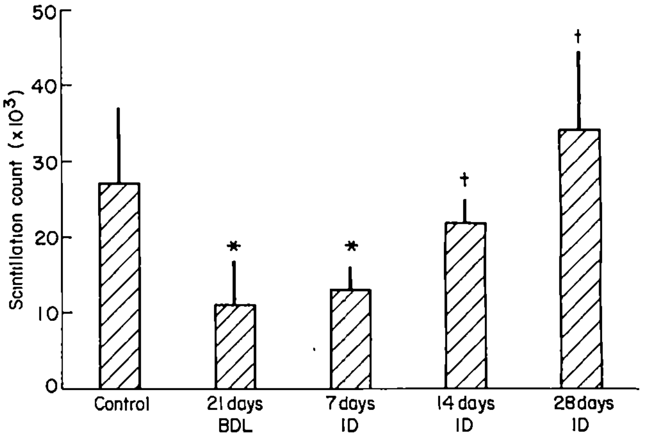

Figure 3 *Mean lymphocyte stimulation (scintillation count) following internal biliary drainage (ID). Bars show 95 per cent confidence limits* *P<0·05 *compared with controls,* †P<0·05 *compared with 21-day bile duct ligation (BDL)*

Mortality

There was no mortality for BDL animals at 7, 14 or 21 days; at 35 days mortality rate was 30 per cent and attempts to go beyond 35 days were associated with higher and unacceptable mortality rate. Dead animals had cirrhotic changes in the liver, ascites and weight loss. For the biliary drainage models, ID had an overall mortality rate of 25 per cent, although this was lower at the end of the experiment due to improved technique. Death was invariably due to biliary peritonitis from anastomotic leakage. Mortality for the ED model was much lower because no new anastomosis was performed. Only one animal died in this group after dislocation of the cannula from the distended bile duct.

Lymphocyte function tests

The scintillation counts for animals with experimental biliary obstruction are presented in *Figure 2*. There was no significant difference between lymphocyte stimulation for controls, sham operated or 7-day BDL animals. For BDL at 14 days, 21 days and 35 days there was a significant depression compared with controls ($P<0{\cdot}05$). Regression analysis of scintillation count against the period of jaundice showed a significant negative correlation (correlation coefficient −0·57, $P<0{\cdot}001$). *Figure 3* shows the response to internal biliary drainage. Following BDL

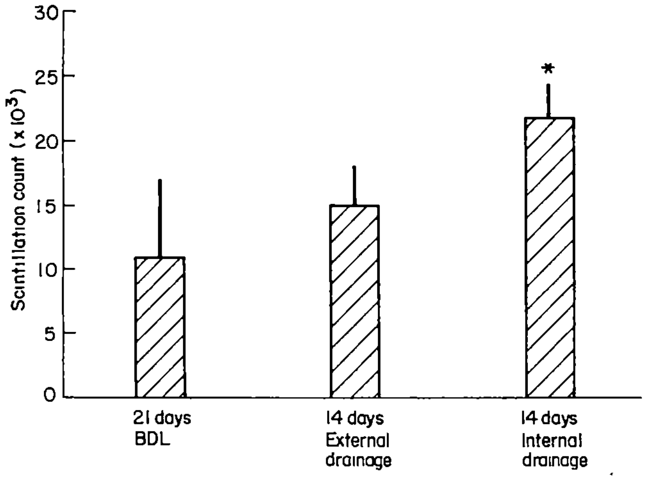

Figure 4 *Mean lymphocyte stimulation (scintillation count) following external biliary drainage. Bars show 95 per cent confidence limits. * $P<0\cdot05$ compared with 14-day external drainage and 21-day bile duct ligation (BDL)*

for 21 days, internal drainage for 7 days did not improve lymphocyte function compared with 21-day BDL animals. However, by 14 days there was a significant improvement compared with the 21-day BDL group ($P<0\cdot05$). After 28 days ID, lymphocyte stimulation returned to control levels. Regression analysis showed a significant positive correlation between lymphocyte stimulation and the duration of relief (correlation coefficient $+0\cdot71$, $P<0\cdot001$).

The results for the externally drained animals are seen in *Figure 4*. Following 14 days ED there was no significant increase in lymphocyte function compared with 21-day BDL animals. A similar group of animals which had ID for 14 days had significantly higher lymphocyte stimulation ($P<0\cdot05$) than ED animals and 21-day BDL animals

Discussion

Patients with obstructive jaundice suffer from a high incidence of septic complications[1] which may occur in up to 72 per cent of those with complicated biliary disorders[2]. The cause of this increased susceptibility to infection is not fully understood, but it may be related to a decrease in immune function. Little is known of the immunological status of patients with biliary obstruction, although cell-mediated immunity has been shown to be reduced in carcinoma of the pancreas[15]. Other forms of liver disease in which there is a degree of cholestasis have demonstrated reduced cell-mediated immunity[16]. Experimental studies have mainly concentrated on the reticuloendothelial system[7]. Other polymorphonuclear cells have also been shown to be impaired[10].

The present study has investigated T lymphocyte dysfunction in an experimental animal model of obstructive jaundice. In agreement with other studies on rats[17] this has confirmed that there is significant T lymphocyte depression after 21 days BDL. The magnitude of this is less in our study; however, there can be considerable intrastrain variation in the response to phytohaemagglutinin[14]. In addition we have shown that this immune suppression develops progressively with no lymphocyte depression in the early stages, despite biochemical evidence of liver dysfunction. This pattern of immune suppression, requiring time to develop, is similar to results reported on Kupffer cell activity[7].

The exact cause of this T lymphocyte depression is unknown; however, it is likely to be multifactorial and may involve a cellular deficit and/or a circulating plasma inhibitory factor. There are numerous candidates for the role of a possible plasma inhibitory factor, present in obstructed animals, which have been shown to inhibit T lymphocyte proliferation *in vitro*. These include bilirubin[18], bile acids[19], endotoxin[20], α-2-globulin[21] and abnormal lipoproteins[22]. Although these factors may have a role *in vivo*, they are unlikely to have a major influence in an *in vitro* assay, as repeated cell washing will remove the effect of any factor which has not become membrane bound. A cellular deficit may involve changes in monocyte antigen presentation or T cell helper/suppressor ratios. Further studies are required to investigate these possibilities.

The present results demonstrate recovery of T lymphocyte function in BDL animals following internal drainage. This recovery is not immediate despite early return of normal biochemical liver function; it requires 28 days before complete restoration of immunocompetence. Residual pathological changes in the liver may account for this prolonged hyporesponsiveness.

External biliary drainage is not as effective as internal drainage in restoring immune function at 14 days. Further studies are required to show if longer periods of external drainage will restore lymphocyte function. The results suggest that an important factor in restoring T lymphocyte responsiveness is returning bile to the gastrointestinal tract.

In summary, experimental biliary obstruction leads to progressive impairment of cell-mediated immunity. This suppression is reversible by prolonged internal biliary drainage External biliary drainage was not found to be as effective as internal drainage.

In conclusion, these results suggest that rapid investigation and management of patients with obstructive jaundice might reduce the incidence of infective complications. They also explain why preoperative external biliary drainage is not as effective in reducing these complications as was originally hoped.

Acknowledgements

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Assessment of the biliary tract after liver transplantation: T tube cholangiography or IODIDA scanning

Biliary tract obstruction or anastomotic leakage are common problems following liver transplantation. In a sequential study, 31 patients with a liver transplant were investigated by ^{99m}Tc-IODIDA (IODIDA) scanning and T tube cholangiography (TTC) and the results were compared with clinical outcome. Seven patients had an extrahepatic biliary obstruction and one patient had a biliary leak. In the detection of biliary complications TTC and IODIDA scanning were similar in terms of sensitivity (63 per cent for both) but TTC had a better specificity (79 per cent versus *60 per cent) and accuracy (74 per cent* versus *60 per cent) than IODIDA scanning. When liver function was taken into account, the diagnostic efficacy of both tests in patients with bilirubin levels of <200 μmol/l was similar. With levels >200 μmol/l there was a greater number of false positive results with IODIDA scanning (12 per cent* versus *54 per cent). The only significant biliary leak was clearly detected by TTC but not IODIDA scanning. TTC remains the more effective way of evaluating the biliary tract after transplantation. IODIDA scanning has limited value when bilirubin levels are elevated, but may provide additional information about blood supply, hepatocyte function and intrahepatic cholestasis.*

Keywords: Liver transplantation, biliary tract reconstruction, biliary anastomosis, biliary tract complication, T tube cholangiography, biliary scintigraphy, ^{99m}Tc-IODIDA scintiscanning

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Improvement in surgical technique and use of low-dose steroids have resulted in fewer biliary tract complications following liver transplantation[1–5]. Nearly one in five patients still experiences problems[4,6] and assessment of the biliary tract is performed routinely 7 days post-transplantation and later if clinically indicated Cholangiography (T tube, percutaneous transhepatic or endoscopic retrograde) has proved useful in demonstrating the type, location and severity of most early and late biliary complications[7]. Injection of contrast into the biliary tree is frequently related to episodes of cholangitis and bacteraemia[8,9] which are especially dangerous in immunosuppressed patients. Investigation is more difficult when the patient does not have a T tube.

Hepatobiliary scintigraphy is a non-invasive, widely available and inexpensive technique. In addition to identifying biliary tract complications it may provide useful information about hepatocyte function and intrahepatic cholestasis[10,11]. IODIDA (Solcoscint IODIDA, SOLCO Balse Ltd., Birsfelden, Switzerland) has a lower urinary and higher biliary excretion and has significant advantages over other ^{99}Tc-Sn-2,6-diethylacetanilidoimmodiacetate (HIDA) derivatives especially when bilirubin levels exceed 80–100 μmol/l[12–15]. It has been advocated in diagnostically difficult situations such as liver transplant, bile duct reconstruction, suspicion of bile leakage, examination in small children or of critically ill patients.

A prospective study was undertaken to compare the diagnostic value of ^{99m}Tc-IODIDA isotope (IODIDA) scanning and T tube cholangiography (TTC) in patients after liver transplantation

Patients and methods

Thirty-one liver transplant patients underwent TTC and hepatobiliary scintigraphy Assessment was performed routinely in 26 patients between 7 and 10 days after surgery and at a later stage in five patients when suspicion of complications arose. Both tests were performed within 48 h and no change in the clinical situation was observed in any patient between the two studies.

The indications for liver transplantation were: primary biliary cirrhosis in 12 patients, fulminant hepatic failure in six, chronic active hepatitis in four, sclerosing cholangitis in three, α-1-antitrypsin deficiency in two, cryptogenic cirrhosis in two, hepatocellular carcinoma in one and alcoholic cirrhosis in one. There were two children (aged 1·5 and 7 years) and 29 adults whose mean age was 40·7 years (range 18–68 years) Seventeen of the group were female.

The types of biliary reconstruction used are shown in *Figure 1*. (a) end-to-end choledochocholedochostomy in 16 patients (52 per cent), (b) gallbladder conduit in 11 (36 per cent), (c) choledocho-Roux-en-Y-jejunostomy in three cases (10 per cent), and (d) in one case a conduit to jejunum (3 per cent).

Bilirubin levels at investigation ranged from 25 to 883 μmol/l and were less than 100 μmol/l in nine patients, less than 200 μmol/l in 15 patients and greater than 200 μmol/l in the remaining 17 cases

Both imaging studies were reported independently by an examiner who did not have access either to clinical information or to the results of the other test. The T tube cholangiograms were read 'blind' by a consultant radiologist with experience in examining transplanted patients (F B.) and the IODIDA scans were read 'blind' by a nuclear medicine specialist (S.L)

Scintigraphy method

After fasting for at least 4 h 80 MBq of commercially available IODIDA were injected as a bolus into an antecubital vein With the patient supine, images of the abdomen were obtained using a large field of view γ-camera with a low-energy all-purpose collimator and recorded on computer at one frame/min for 40 min Analogue film images were also obtained every 5 min over this same interval. Further images were obtained at 1–4 h and 18–24 h if IODIDA clearance was delayed or a leak suspected

The results of scintigraphy were classified as follows·

1 *No obstruction* no obstruction to the flow of the scintigraphic agent into the bowel taking into account normal variation[16]
2 *Partial obstruction.* detection of partial obstruction was primarily

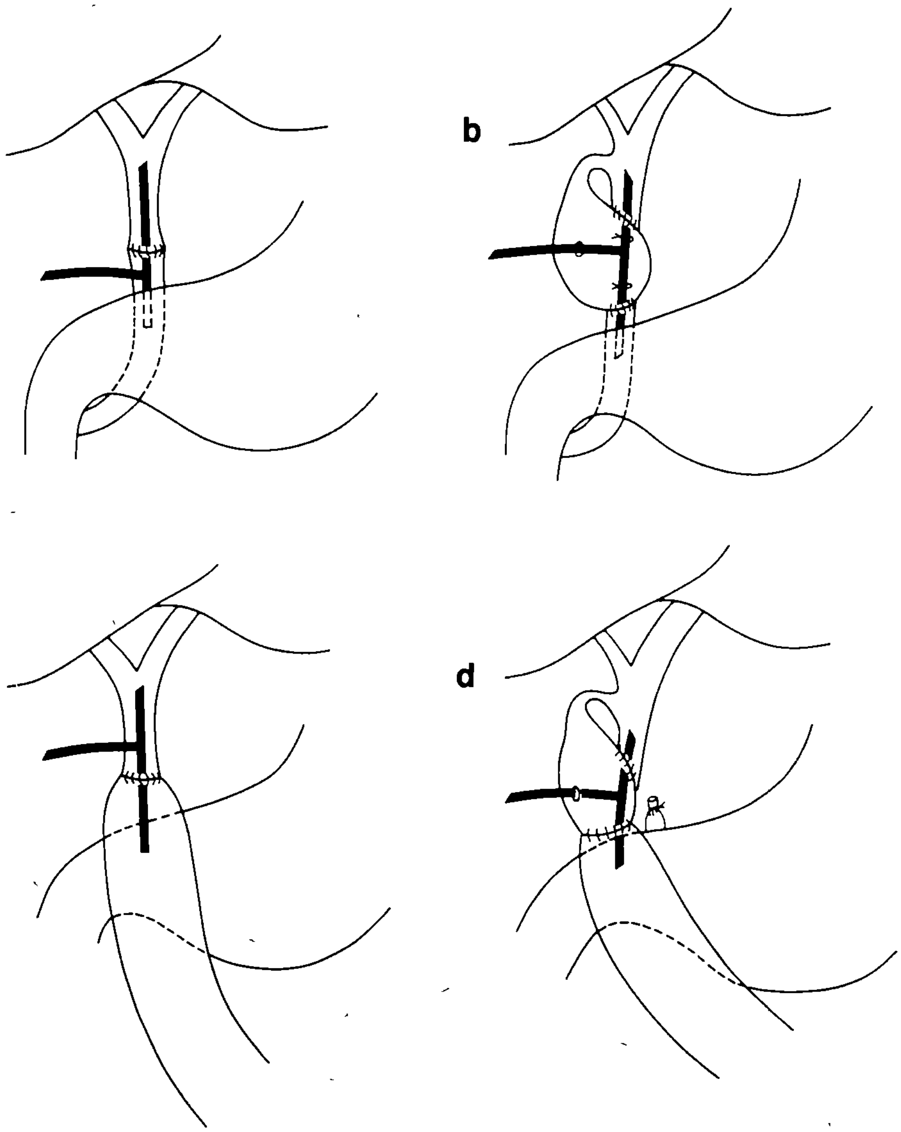

Figure 1 *Schematic diagram showing the types of biliary reconstruction used in 31 liver transplant recipients·* **a** *end-to-end choledochocholedochostomy,* **b** *choledochocholecystcholedochostomy,* **c** *Roux-en-Y choledochojejunostomy,* **d** *Roux-en-Y choledochocholecystjejunostomy*

based on filling defects in narrowing of the common bile duct or bile pooling in the segmental ducts[17] and a delay of 60 min or more before appearance of isotope into the bowel

3. *Complete obstruction* absence of the scanning agent from the small bowel after 24 h regardless of whether or not images of the bile duct had appeared[18–20]
4. *Presence or absence of biliary leak·* the appearance of radioactivity in the peritoneal cavity.

Information was available on impaired hepatic uptake of radionuclide indicating primary hepatic dysfunction and intrahepatic cholestasis manifested by relatively good uptake of IODIDA, delayed visualization of intestine between 4 and 24 h and visualization of the bile duct adequate to rule out extrabiliary obstruction[21,22]

T tube cholangiography (*TTC*)

TTC was performed with antibiotic cover. Approximately 20–30 ml urografin 325 were slowly injected during screening to display as much of the duct system as possible and to avoid discomfort, overfilling of the duct or bacteraemia If contrast ran freely through the lower duct (or conduit) into the bowel without showing the upper ducts, a repeat injection was performed with the patient in head-down position

The results of TTC were classified as follows:

1. *No obstruction* no obstruction to the flow of contrast into the bowel with non-dilated intrahepatic ducts
2. *Partial obstruction* the presence of strictures or filling defects within the extrahepatic or intrahepatic bile ducts causing delay in passage of contrast into the bowel.
3. *Complete obstruction* obstruction to the passage of contrast either into the bowel or alternatively from common hepatic duct to intrahepatic ducts
4. *Presence or absence of a leak.*

In addition to scintiscanning and radiological examination all patients underwent detailed clinical monitoring, biochemical assessment, protocol liver biopsy on day 7 post-transplant and later if required. The ultimate assessment of the biliary tract and final diagnosis were based on the patient's clinical course and information which became available either through reoperation or autopsy.

Results

No biliary tract complications were found in 23 patients (74 per cent), seven had extrahepatic obstruction (23 per cent) and one had a biliary leak (3 per cent). The process of final diagnosis is shown in *Table 1*.

T tube cholangiography (*TTC*)

In the 23 patients without biliary complications T tube cholangiograms were reported normal in 18. There were five false positive studies in which the diagnosis of either complete or partial obstruction was made. Three of these patients had a gallbladder conduit. in two of these the diagnosis of complete obstruction of the upper choledochocholecystanastomosis had been made (*Figures 2a* and *b*) and in one partial obstruction at the papilla with proximal dilatation was reported. The fourth patient had a duct-to-duct reconstruction and partial

Table 1 *Means of verification of the final diagnosis in 31 cases*

	Final diagnosis		
	Autopsy ($n=5$)	Operation ($n=7$)	Clinical course ($n=19$)
Biliary leak ($n=1$)	1	–	–
Obstruction ($n=7$)			
Inflammation of conduit	1	–	–
Anastomotic stenosis	1	2	–
Biliary sludge	3	–	–
No biliary complications ($n=23$)	4	2	17

obstruction of the anastomosis was suspected. In the remaining patient with a choledochojejunal reconstruction, a proximal non-anastomotic obstruction was diagnosed. In none of these patients did the liver function tests, histology or clinical outcome indicate any clinically relevant biliary obstruction during 2–24 months of follow-up. The patient with the biliary leak was correctly diagnosed on T tube cholangiogram.

In the seven patients with extrahepatic biliary obstruction, four were shown on the T tube cholangiograms. There were three false negative studies. Two were in patients with a duct-to-duct anastomosis. In the first of these patients a hepatic artery thrombosis was diagnosed on ultrasonography and confirmed angiographically. Reoperation showed an anastomotic stricture and the anastomosis was converted to a Roux-en-Y choledochojejunostomy. In the second patient a papillotomy was performed and biliary sludge was removed 2 weeks after the TTC (*Figures 3a* and *b*). The other patient with a false negative study had a gallbladder conduit. Reoperation because of clinically increasing cholestasis and abdominal pain revealed obstruction of the common bile duct due to inflammation of the conduit and after cholecystectomy a Roux-en-Y choledochojejunostomy was performed. When the studies were reassessed in the light of full clinical information no changes in the radiological diagnosis were made ruling out an error in the interpretation of the images.

IODIDA scanning

In one of the 23 patients without proven biliary complications there was poor hepatic uptake of IODIDA indicating pure hepatocellular dysfunction and the biliary tract was not visualized. In the other 22 normal patients, 13 were reported to have normal scans. There were nine false positive scans. Six were reported as completely obstructed. Four of these patients had histologically proven moderate rejection, one had mild rejection and pneumonia and one had severe sepsis. Three scans were reported as partially obstructed on the basis of delayed appearance of radioactivity in the gut and poor delineation of the biliary tract. One of these patients had moderate rejection on biopsy, one had sepsis and mild rejection and one had an intra-abdominal abscess. The mean bilirubin level of the nine patients with false positive results was more than twice that of patients with true negative IODIDA scanning results (*Figure 4*). The false positive rates for IODIDA scanning and TTC were 54 per cent and 14 per cent when the bilirubin level was >200 μmol/l and 12 per cent and 18 per cent when the level was <200 μmol/l.

Scintiscanning failed to detect leakage of isotope into the abdominal cavity in the patient with a biliary leak.

In the seven patients who were eventually shown to have biliary obstruction IODIDA scanning correctly diagnosed five. There were two false negative studies. Both patients had a duct-to-duct anastomosis and were diagnosed as having enlarged but unobstructed ducts and showed appearance of radioactivity in the gut within 35 min. Evidence of obstruction was found in both and corrected by reoperation in one and endoscopic dilatation in the other.

Again no changes in the diagnosis were suggested after unblinded review of the images when clinical information was available.

The diagnostic accuracy of TTC and IODIDA scanning in predicting eventual clinical outcome is shown in *Table 2*. Both

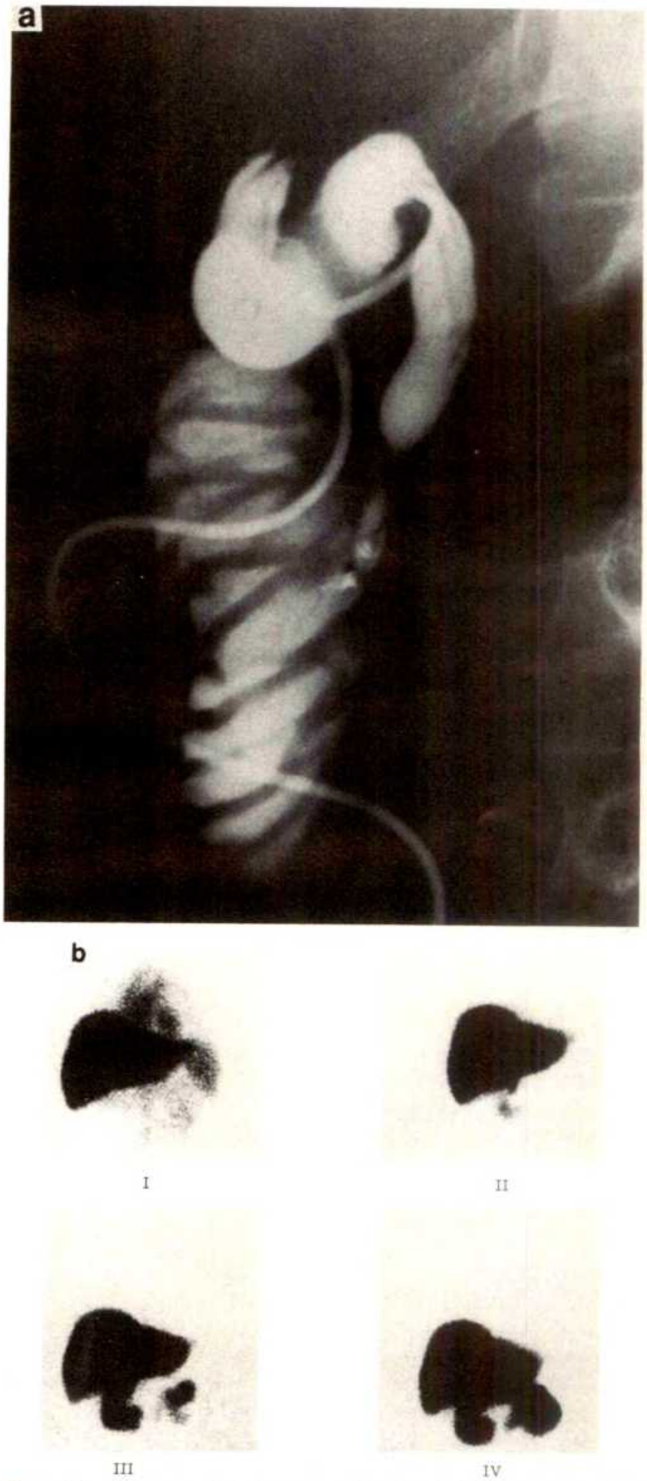

Figure 2a *Example of a false positive T tube cholangiogram probably due to underfilling of the biliary system in a patient with a gallbladder conduit reconstruction. The study was performed 27 days after transplantation due to deterioration of the liver function tests (bilirubin was 60 μmol/l and alkaline phosphatase was 970 units/l). In this patient the cholangiogram was reported as a complete obstruction of the donor common bile duct to donor gallbladder anastomosis. No obstruction was confirmed in the follow-up period.* **b** *Selected anterior views from IODIDA study obtained at (I) 2–5 min, (II) 17–20 min, (III) 27–30 min and (IV) 35–38 min after injection. They show good extraction of IODIDA from the blood pool (activity within the heart is seen only on the image at 2 min) and normal clearance from parenchyma into the gastrointestinal tract*

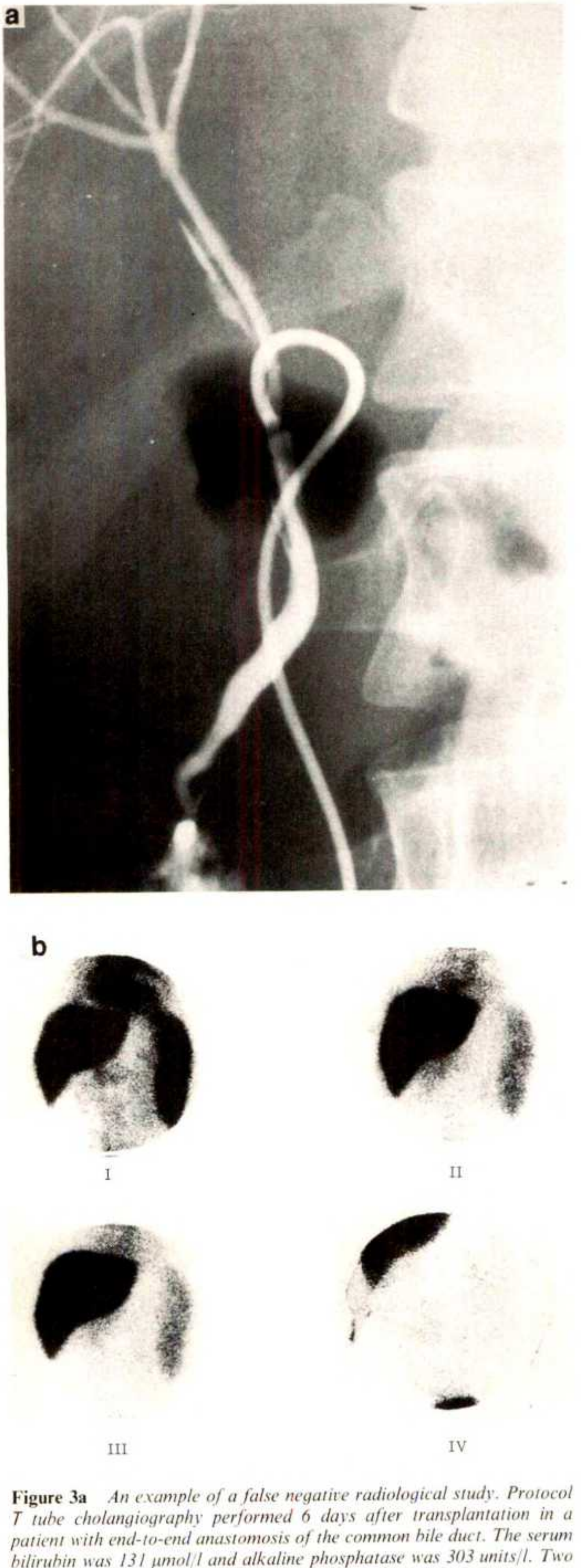

Figure 3a *An example of a false negative radiological study. Protocol T tube cholangiography performed 6 days after transplantation in a patient with end-to-end anastomosis of the common bile duct. The serum bilirubin was 131 µmol/l and alkaline phosphatase was 303 units/l. Two weeks later this patient was submitted to an endoscopic papillotomy and biliary sludge was removed from the common bile duct.* **b** *Selected anterior views from IODIDA study obtained at (I) 2–5 min, (II) 27–30 min, (III) 1 h and (IV) 24 h after injection. Prolonged retention of activity in the blood pool, heart and other vascular structures, relatively good uptake by the graft and absence of excretion into gastrointestinal tract indicates obstruction*

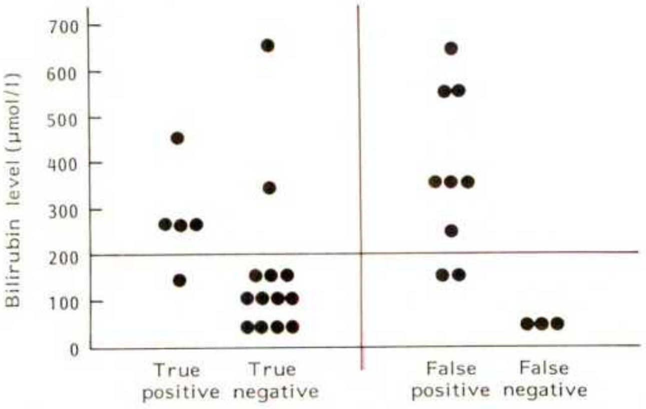

Figure 4 *Comparison of the results of IODIDA scanning study and bilirubin levels*

Table 2 *Comparison of the sensitivity, specificity and accuracy of TTC and IODIDA scanning in the diagnosis of biliary tract complications after liver transplantation*

	Sensitivity (%)	Specificity (%)	Accuracy (%)
TTC (all patients)	63	78	74
TTC (EECC, $n=16$)	67	92	88
TTC (GBCD, $n=11$)	50	57	55
IODIDA (all patients)	63	59	60
IODIDA (EECC, $n=16$)	50	67	62
IODIDA (GBCD, $n=11$)	100	88	90

TTC, T tube cholangiography; IODIDA, ^{99m}Tc-IODIDA scanning; EECC, end-to-end anastomosis of common bile duct; GBCD, gallbladder conduit reconstruction

tests had similar sensitivity but TTC had a better specificity and accuracy than IODIDA scanning. The only biliary leak was clearly shown on TTC but not identified on IODIDA scanning.

The diagnostic value of the tests in the detection of biliary obstruction was influenced by the type of biliary reconstructive procedure. TTC was more accurate than IODIDA scanning in detecting obstruction in patients with end-to-end choledochocholedochostomy, but in those with a gallbladder conduit IODIDA scanning was more efficient (*Table 2*). When the liver function tests did not show cholestasis, combination of the results of TTC and IODIDA increased the sensitivity to 85 per cent and specificity to 91 per cent with an accuracy of 90 per cent.

Discussion

Liver transplant recipients are susceptible to a wide variety of complications which may threaten allograft and patient survival[5,23]. Biliary complications, hepatic preservation injury, rejection, hepatic artery thrombosis and infection may all lead to a rapid deterioration in liver function. Differentiating between the causes may prove difficult.

Early diagnosis of biliary complications is important in planning treatment and because other post-transplant problems are often diagnosed by exclusion[24]. Oral cyclosporin is poorly and unpredictably absorbed from the intestine during bile diversion[25]. Exclusion of biliary complications as a cause of deteriorating liver function allows early clamping of the T tube, with re-establishment of the enterohepatic circulation.

Our results have shown that the sensitivity of both tests is similar but TTC has a better specificity and overall accuracy than IODIDA scanning.

In patients with bilirubin levels above 200 µmol/l a greater number of false positive results appeared with IODIDA scanning because of misdiagnosed intrahepatic cholestasis due to rejection or sepsis. Hepatobiliary scintigraphy can provide accurate information in the evaluation of cholestasis[22,26] but this is difficult in patients with underlying intrahepatic disease where extrahepatic obstruction is suspected. In the transplant patients rejection affects small bile ducts leading to intrahepatic cholestasis[24,26] which can mimic complete biliary obstruction[27]. Six out of nine of our false positive studies showed this pattern. In the remaining three patients, poor visualization of the biliary tract and delayed intestinal appearance made scintigraphic interpretation equivocal as ductal delineation was inadequate. We found that in this group of patients, with bilirubin levels over 200 μmol/l, IODIDA scanning had a very low specificity and overall accuracy. Discrimination between high grade obstruction and severe intrahepatic disease based on the image pattern was not possible and suggests that the level of obstruction in such a case must be made by other modalities.

The accuracy of TTC is not influenced by a high serum bilirubin level or by graft dysfunction. TTC does, however, require meticulous technique if cholangitis and bacteraemia are to be avoided. Required low pressure injection can result in underfilling of the biliary tract as can rapid emptying of contrast into the intestine through a widely patent biliary–enteric anastomosis. Underfilling may explain at least three of five false positive studies especially in the patients with gallbladder conduits and combination of the results of TTC and IODIDA scanning in these cases may be helpful if severe cholestasis is not present.

The many pitfalls encountered with scintigraphy in the differential diagnosis of jaundice with high bilirubin levels undermines its usefulness as a first choice diagnostic procedure after transplantation. Scintigraphy can play an adjuvant role and be of considerable clinical value in cases where technical difficulties yield indeterminate TTC results such as with a gallbladder conduit anastomosis. In spite of its limitations, TTC still remains the most effective means of evaluating the biliary tract after transplantation. IODIDA scintiscanning may provide important information about the biliary tract and graft function with bilirubin levels below 200 μmol/l, but is unreliable in the presence of rejection, sepsis or when bilirubin levels exceed 200 μmol/l.

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Regional chemotherapy for colorectal liver metastases: a phase II evaluation of targeted hepatic arterial 5-fluorouracil for colorectal liver metastases

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The results of systemic chemotherapy in patients with liver metastases from colorectal cancer remain dismal. Regional chemotherapy has been advocated as a method of improving the delivery of cytotoxic drugs to tumour, while minimizing systemic toxicity. The use of vasoactive agents to redistribute arterial blood flow towards tumour, and of biodegradable microspheres to slow tumour blood flow, have also been suggested as methods of further improving tumour exposure to drug. We present 21 patients who received intrahepatic arterial chemotherapy for colorectal liver metastases. Combined treatment (angiotensin II, albumin microspheres and 5-fluorouracil) was administered 4–6 weekly, and bolus 5-fluorouracil was given in the intervening weeks. Toxicity was minimal. Responses were seen in seven patients. Fewer than half of the deaths were from liver metastases; a quarter of the patients died from non-cancer-related causes. Survival was prolonged in the treated group compared with historical controls. These results suggest that this regimen has activity in patients with colorectal liver metastases.

Keywords: Liver metastases, 5-fluorouracil, microspheres

There are more than 6000 deaths from colorectal cancer per annum among patients aged less than 70 years in the UK. More than 60 per cent of patients with recurrent colorectal cancer die with liver metastases; in one in five patients, disease is restricted to the liver[1]. Survival after diagnosis of liver metastases is limited; in our institution the mean survival of patients with multiple bilateral metastases is 3 months[2].

In this situation, systemic chemotherapy using conventional cytotoxic agents has been shown to be relatively ineffective. In the absence of a more specific chemotherapeutic agent for colorectal cancer, attention has focused on attempts to improve tumour exposure to the anticancer drugs that are currently available.

Three levels of tumour targeting have been described: (1) selective drug delivery to the tumour-bearing organ (i.e. regional chemotherapy); (2) drug delivery biased to tumour rather than to normal liver; and (3) enhancement of uptake of cytotoxic drug by the cell[3]. A combined approach to improve both first and second order targeting is now feasible.

We describe our experience of regional chemotherapy in patients with colorectal liver metastases. All patients received angiotensin II and albumin microspheres in addition to intrahepatic arterial 5-fluorouracil. Both of these agents have been shown to improve second level targeting. Angiotensin II is a vasoactive agent known to redistribute arterial blood flow towards tumours[4]. Biodegradable microspheres have previously been shown to slow tumour blood flow and to enhance tumour drug uptake[5]. Therefore, by combining the two, it is possible that microsphere delivery to the tumour would be increased, thereby selectively reducing tumour blood flow and increasing the probability of drug uptake.

Patients and methods

Albumin microspheres were made 'in house' under sterile conditions by a technique involving stabilization by glutaraldehyde of a water-in-oil emulsion containing protein[6]. Three hundred and eighty milligrams of human serum albumin (Sigma Chemical Co. Ltd., Poole, UK) was dissolved in 800 μl water containing 2 mg sodium dodecyl sulphate. This constituted the disperse phase of a water-in-oil emulsion. Water droplets were stabilized by the addition of 240 μl 15 per cent glutaraldehyde solution, and the resulting spherical particles were separated and washed in petroleum ether and isopropanol. The microspheres were reconstituted in phosphate-buffered saline containing 0·5 per cent Tween 80 (Sigma). Following mesh filtration and differential centrifugation, microspheres of between 20 and 40 μm in diameter (50 per cent weight average) were obtained. Particles of this diameter were selected because they are known to embolize within the first capillary bed encountered and to biodegrade over 48 h (Reference 7).

A pilot study looking at the toxicity of incremental doses of microspheres had shown that a hepatic arterial bolus injection of 300 mg albumin microspheres (containing approximately 6×10^7 particles) produced mild right upper quadrant pain and nausea. Doses greater than this caused more severe hepatic pain; therefore 300 mg was used in subsequent treatments.

Twenty-one patients with colorectal liver metastases (mean(s.d.) age 59 (8) years, range 41–71 years) have been included in the study. Two patients had between 10 and 25 per cent hepatic replacement; nine had between 25 and 50 per cent hepatic tumour burden; and in ten patients the volume of disease was greater than 50 per cent as measured by albumin colloid scan. Liver metastases were found in 11 patients at the time of initial presentation. In the remaining patients, liver metastases were discovered during follow-up; in four, these metastases were discovered while the patient was still asymptomatic.

All patients had surgical placement of a hepatic arterial perfusion catheter which consisted of a silicone catheter and subcutaneous resealable injection port. In patients with a standard arterial anatomy, the catheter was implanted into the gastroduodenal artery so that the tip lay at its orifice from the hepatic artery. Thus, infusions through the catheter were delivered to the liver via the hepatic arterial stream. In patients with a dual arterial supply, two catheters were inserted, a saphenous vein graft being used to hold the catheter where no suitable hepatic arterial side-branch existed[8].

Chemotherapy was commenced as an outpatient procedure. 5-Fluorouracil was given in conjunction with the vasoactive agent angiotensin II and albumin microspheres. An infusion of angiotensin II was commenced via the catheter at a rate of 10 μg per minute; 100 s later, a bolus injection of microspheres, followed by 1 g 5-fluorouracil, was given via the catheter. Microspheres were available for

Table 1 *Number of patients suffering from nausea, vomiting or epigastric pain during treatment or from raised liver enzymes or myelosuppression at 1 week after combined therapy (angiotensin II, albumin microspheres and 5-fluorouracil) and regional 5-fluorouracil*

	Combined therapy ($n=21$)	5-Fluorouracil ($n=21$)
Nausea/vomiting		
Mild	8 (38)	0
Moderate	4 (19)	0
Acute epigastric pain		
Mild	9 (43)	0
Increased liver enzymes	0	0
Myelosuppression*	2 (10)	2 (10)

Values in parentheses are percentages; * myelosuppression is defined here as white cell count $<3000/\text{mm}^3$ and platelet count $<100\,000/\text{mm}^3$

administration at monthly intervals. Between combination treatment, 1 g 5-fluorouracil was given weekly as a bolus injection through the catheter.

Side-effects were recorded; full blood-count and liver function tests were performed weekly.

The response to therapy was assessed every 8–12 weeks by ultrasonography. Standard response criteria were used to measure response (complete response where no evidence of disease remained; partial response where a 50 per cent reduction in disease occurred by two diameters; minimal response when between 25 and 50 per cent reduction in disease was seen by two dimensions; static disease where there was no change; progression when an increase in tumour size was recorded).

Results

The mean duration of therapy was 7·4 months. Toxic side-effects were few. *Table 1* summarizes the toxicity associated with either combined regional therapy or regional 5-fluorouracil alone. Acute pain, nausea and vomiting occurred only during the combined treatment.

One patient was of particular interest. Before operation angiography demonstrated normal arterial anatomy and a catheter was inserted in the standard fashion. Unfortunately, hepatic arterial perfusion scintigraphy after operation showed that only part of the liver was being perfused by this route; in effect, the right lobe of the liver received regional chemotherapy, whereas the left lobe was exposed only to drug that had passed through the right lobe and had entered the systemic circulation (i.e. systemic therapy). Ultrasound assessment demonstrated disease progression in the region of liver receiving systemic treatment, whereas the tumour in the area of liver receiving regional therapy responded. The patient remains alive after 35 months of treatment. This case is described in detail elsewhere[9].

Of the remaining 20 patients, one had a partial response, five had minimal response and three had stable disease. Disease progression occurred in 11 patients during therapy.

Of the 18 deaths, eight patients died from progressive disease, four from extrahepatic tumour (periportal lymph nodes, small intestine, lung and bone) and one from local recurrence with ureteric involvement. One patient died from respiratory complications following a secondary laparotomy for intestinal obstruction due to adhesions, and four died from intercurrent disease, including myocardial infarction, gastrointestinal haemorrhage (peptic ulceration), pancreatitis and an acute febrile illness while abroad.

The median survival from the time of diagnosis was 9 months; 20 per cent of patients survived for more than 18 months (*Figure 1*). Three patients remain alive and well at 8, 25 and 35 months, respectively.

Discussion

In theory, regional chemotherapy should enhance tumour drug delivery while reducing systemic exposure and hence toxic side-effects. However, bolus intra-arterial 5-fluorouracil alone has been shown to have no impact on systemic drug levels[10].

Coadministration of biodegradable starch microspheres with a half-life of approximatly 20 min has been shown to improve the regional advantage of arterially administered cytotoxic agents[11]. The microspheres are thought to act by slowing arterial blood flow within the liver, thereby increasing the time available for drug uptake by tissue within the target organ. It has been suggested that improved drug uptake with arterial blockade might be improved by using embolic particles with a longer half-life. Thus the albumin particles used in this study might be expected to confer an additional advantage.

Previous results in both patients and animal models have suggested that tumour blood flow may be temporarily increased by an infusion of vasoactive agents[11–15]. The mechanism is thought to involve arteriolar constriction in the normal tissue surrounding tumour, causing a passive increase in tumour perfusion[16]. Sasaki and colleagues[4] showed that blood flow to intrahepatic tumour could be increased by up to four times basal levels during an angiotensin II infusion. The peak effect was found to be after 100 s of a regional infusion of 10 μg/min. We have recently confirmed these findings[17,18].

Although the median survival of patients with widespread liver metastases in the present study is approximately three times that of historical controls[2], there are a number of factors that might bias the results. Clearly, there was an element of selection for regional therapy. Furthermore, the few asymptomatic patients included in the study might have caused some distortion of the results because of 'lead time' gained between the 'screening' investigation and the onset of symptoms.

Nevertheless, there is probably a modest improvement in survival. In the patient described, in whom regional chemotherapy was compared with systemic treatment, with the patient acting as his own control, tumour regression occurred only in the segment of liver receiving regional chemotherapy. Furthermore, it would appear that the pattern of disease in this group of patients has been altered; fewer than half of the patients died from liver metastases.

Further improvements in the therapeutic index may be possible. Cytotoxic drug-loaded particle formulations which act as slow-release preparations have been synthesized for a variety of chemotherapeutic agents, including mitomycin C, Adriamycin® (Farmitalia Carlo Erba Ltd., St. Albans, UK), 5-fluorouracil and cisplatin. We have previously shown that Adriamycin-loaded microspheres are trapped in rabbit kidney and liver following regional administration[19], leading to a marked reduction in systemic exposure and maintenance of high drug levels within the target organ[7]. The drug-release characteristics can be modified to optimize the pharmacological profile of cytotoxic particles. Escalation of drug dosage is clearly possible because of the reduced systemic toxicity associated

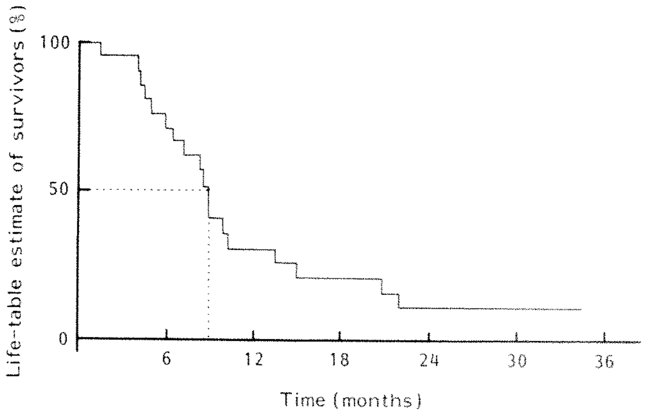

Figure 1 *Life-table derived from 21 patients with colorectal liver metastases who received regional 5-fluorouracil albumin microspheres and angiotensin II. Median survival is estimated at 9 months*

with microencapsulated chemotherapy. Eventually either rising systemic drug levels or hepatotoxicity are likely to limit this approach, although any improvement in tumour drug exposure may be clinically useful in view of the steep dose–response curve associated with cytotoxic drugs. This effect could be further amplified by tumour targeting with vasoactive agents.

This study shows that targeted microsphere-based regional chemotherapy is associated with prolongation of survival compared with historical controls. The differential response to regional and systemic chemotherapy in the patient described and the alteration in the pattern of mortality suggest that this benefit, although modest, is probably real. Additional techniques to improve the therapeutic advantage of regional chemotherapy, including drug-loaded particles and vasoactive agents, require further evaluation to define their clinical role in the treatment of colorectal liver metastases.

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Hepatic metastases from colorectal carcinoma: impact of surgical resection on the natural history

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From 1960 to 1987, 1209 patients with colorectal liver metastases were recorded, and followed until 1 January 1990. In 242 cases the diagnosis was based on external imaging, whereas 967 patients had operative confirmation and staging of their liver disease. Three groups of patients were analysed: group 1 involved 921 cases, of whom 902 were deemed non-resectable whereas 19 could not be unequivocally classified. Only 21 patients lived for longer than 3 years, seven survived for 4 years, but there were no 5-year survivors. Group 2 comprised 62 highly selected patients who at laparotomy demonstrated resectable metastasic spread confined to the liver, but this was not treated mainly because of a formerly different therapeutic approach. These patients had a significantly longer median survival time (14·2 versus *6·9 months), but also failed to achieve 5-year survival. The 226 patients forming group 3 underwent hepatic resection with intent to cure. Nine of them had minimal macroscopic disease left, and 34 with all gross tumour removed had positive margins. Survival of patients with these 43 eventually non-radical resections followed an identical course as in group 2 (median survival 13·3 months, maximum 42 months). Of the 183 patients with potentially curative resection ten died after surgery (5·5 per cent). Actuarial 5 and 10-year survival rates in the remaining 173 patients were 40 and 27 per cent with 25 and seven patients alive at respective periods of time. Until 1 January 1990, 64 patients remained free from recurrent disease for up to 24 years. In three patients the tumour status at death was unclear. The other 106 patients developed definite cancer relapse. Nevertheless they demonstrated a prolongation of survival time by a median of 1 year when compared with the 43 non-radically resected patients or the 62 untreated patients with resectable liver-only metastases, and accomplished a maximum survival time of 8 years. Radical excision of colorectal secondaries to the liver therefore offers effective palliation, and in a small number the chance of a cure.*

Keywords: Colorectal cancer, liver metastases, curative resection, natural history, prognosis, treatment failure

Hepatic resection for colorectal metastases has been reported in several recent series with low mortality rates and 5-year survival figures ranging from 16 to 52 per cent[1–9]. The concept of aggressive surgical treatment of metastatic disease is, nevertheless, not generally accepted. Because favourable results may be due to patient selection rather than a different therapeutic strategy[10,11], prospective randomized trials have been suggested[12–15]. However, it would be difficult to obtain informed consent from patients randomized to no treatment despite resectable disease and, in view of reported results of surgical resection, it is unlikely that ethical committees would agree to such a trial[11,13].

To resolve the uncertainty regarding the value of hepatic resection, we have reviewed a consecutive series of 1221 patients with hepatic metastases from colorectal cancer, who have been prospectively recorded over a 28-year period. The data were analysed to try to answer the following questions. First, can hepatic resection lead to long-term survival and, if so, are there clear selection criteria? Second, can long-term survival also be expected in patients with potentially operable disease who receive no treatment? Finally, has the increased resection rate over the past decade altered the survival pattern?

Patients and methods

From 1960 through 1987, a total of 5249 patiens with colorectal carcinoma were recorded at the Department of Surgery, Erlangen University Hospital. Twelve patients had liver involvement discovered at autopsy, and they are excluded from further analysis. In life, hepatic metastases were detected in 1209 patients: 736 men and 473 women with an age range of 22–91 (median 60) years. They were documented at initial presentation in 713 (59 per cent) patients and during follow-up in the other 496 (41 per cent). In 967 cases (80 per cent) the hepatic involvement was discovered at, confirmed, or treated by means of laparotomy. Of the patients presenting more recently, 242 showed evidence of metastatic spread based on ultrasound examination or computed tomography, often accompanied by carcinoembryonic antigen elevation, but were not considered candidates for surgical exploration.

In 179 patients (15 per cent) the primary procedure was performed in other hospitals. In turn, 22 patients (2 per cent), who had initial treatment in our unit, underwent surgery for hepatic metastases elsewhere, involving liver resection in three cases. These 22 patients are included so as not to eliminate eventual long-term survival in untreated patients.

Adequate external imaging and detailed operative records allowed a reliable judgement of resectability with respect to both hepatic involvement and overall tumour extent in all but 19 cases. Three subsets

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of patients were identified: group 1 involved 921 patients (76 per cent) of whom 902 were deemed not resectable. This was due to extensive liver involvement in 509 cases and to extensive extrahepatic spread, or both, in 393 cases. In addition a small subgroup of 19 untreated patients was included in whom disease confined to the liver could not be unequivocally classified as to resectability. Twenty-three patients in group 1 underwent palliative debulking procedures, and 113 received an arterial catheter for subsequent regional chemotherapy, but they all had non-resectable gross tumour left in place. Group 2 comprised 62 patients (5 per cent) in whom hepatic resection seems in retrospect to have been technically feasible and oncologically useful according to currently accepted criteria (i.e. radical excision of the primary growth, no extrahepatic disease, between one and three liver secondaries). Eight of these patients received intra-arterial chemotherapy, but the others remained untreated, reflecting the formerly different approach to metastatic tumour. The remaining 226 patients (19 per cent) formed group 3, and underwent putative curative resection of the liver secondaries. Almost half of them (109 patients) had simultaneous extrahepatic surgery. This involved the primary tumour in 84 patients, a local recurrence in eight, a solitary nodule in the omentum in five, an isolated peritoneal deposit in three, and limited haematogenous spread to other organs in 14 cases. One patient had a second colon cancer and one a renal carcinoma simultaneously removed.

Out of the total series of patients seen with colorectal spread to the liver, the percentage of patients resected with the aim of cure was 4 per cent in the 1960s, 13 per cent in the 1970s and 24 per cent during the past decade.

Follow-up and statistical evaluation

With no patient lost to follow-up, the tumour status on 1 January 1990, or at the time of death, could be defined in all but three cases (*Table 1*). Survival figures were estimated using the Kaplan–Meier product limited method, and checked for statistical significance by means of the log rank test.

Results

Pathological classification following hepatic resection

Of the 249 patients undergoing hepatic resection, 23 (9 per cent) had deliberate palliative debulking, leaving residual tumour in the liver ($n=10$) or at various extrahepatic sites ($n=13$) (primary tumour, five; local recurrence, one; limited peritoneal seedings, four; distant metastases, eight). Of the 226 group 3 patients, in one case each a non-resectable tumour nodule in the liver remnant, an extensive tumour thrombus in the portal vein, and massive hepatic vein invasion became evident at the very end of the procedure, whereas in six cases some extrahepatic disease could not be completely removed. Thus 217 patients were clinically made tumour-free, but histological examination revealed positive margins in 34 cases (liver, 31; extrahepatic sites, three). Therefore 183 patients (81 per cent of group 3) fulfilled the prime criterion of potentially curative intervention, i.e. removal of all detectable gross tumour with negative margins.

Operative mortality

The 30-day mortality rate for 679 patients who proved to have non-resectable disease at laparotomy was 9 per cent. This includes two deaths in patients undergoing debulking of large masses. The corresponding figure in 242 cases having external imaging only was 8 per cent. However, 31 of the 60 patients who died within 1 month of surgical exploration, and all 20 cases undergoing external imaging, succumbed due to advanced tumour stage, not as a result of treatment or complications. In group 2, three patients (5 per cent) died within 1 month of surgery, two from anastomotic leakage and one from age-related progressive cardiopulmonary deterioration. The mortality rate following putative curative hepatic resection was 5 per cent (ten of 183 patients undergoing radical procedures and two of 43 patients having non-radical intervention). Death was related to the procedure performed on the liver in six patients (surgical complications, three; hepatic failure, three). Anastomotic leakage was the major cause in two cases, acute renal failure in one, and isolated cardiopulmonary complications in three patients. The mortality rate fell from 13 per cent (five out of 39 patients) before 1978 to 4 per cent (seven out of 187 patients) during the past 10 years.

Prognosis

As expected, the 921 group 1 patients had a poor outlook. None survived for 5 years from operative staging or first external imaging, and only 21 (2 per cent) and seven (1 per cent) lived for longer than 3 and 4 years, respectively (*Figure 1*). Nine patients are presently alive at 25–57 months from diagnosis, three of them in the fifth year. There was no significant difference between patients who could and could not be classified with regard to resectability ($P=0{\cdot}78$), and only a trend in favour of the 679 patients undergoing laparotomy compared with the 242 with external imaging only ($P=0{\cdot}06$). Patients with metastatic disease confined to the liver did significantly better than those with distant extrahepatic spread ($P=0{\cdot}0004$), but the differences in median survival times (7·3 *versus* 6·4 months) or 2-year survival figures (12 *versus* 5 per cent) were marginal.

The 62 group 2 patients with untreated resectable disease confined to the liver did considerably better than group 1 patients in terms of median survival time (14·2 *versus* 6·9 months) but also failed to achieve 5-year survival. Three patients are alive at 27, 29 and 46 months.

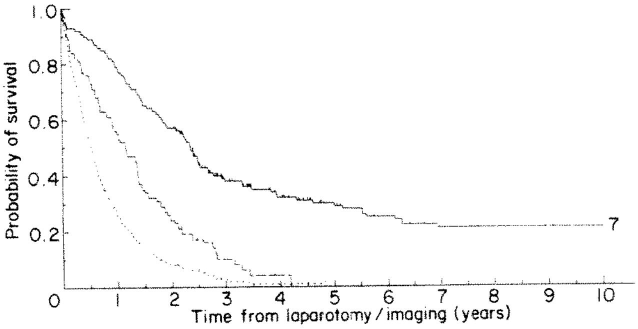

Figure 1 *Survival of patients classified into group 1 (-----, n = 921), group 2 (– – –; n = 62) and group 3 (——; n = 226), including operative deaths. The number at the end of the curve indicates the number of patients surviving beyond 10 years.* $P<0{\cdot}0001$

Table 1 *Outcome and tumour status of 1209 patients with colorectal liver metastases at 1 January 1990*

Patients	Group 1 ($n=921$)	Group 2 ($n=62$)	Group 3 (curative) ($n=183$)	Group 3 (non-radical) ($n=43$)
Alive with no evidence of disease	–	–	54	–
Alive with disease	9	3	14	0
Dead with no evidence of disease	–	–	10	–
Dead with disease	832	56	92	41
Dead, tumour status unknown	–	–	3	–
30-day deaths	80	3	10	2

The 226 group 3 patients had an overall actuarial survival rate of 31 per cent at 5 years, operative mortality included (*Figure 1*). In the subgroup of 43 patients with involved margins ($n=34$) or with small amounts of gross disease remaining ($n=9$), prognosis was poor with median and maximum survival of 13·3 and 42 months, respectively, figures that are similar to those of the resectable but untreated group 2 patients. This was found despite a 63 per cent incidence of solitary metastases among patients undergoing these non-radical procedures. In contrast, patients who met the criteria for curative resection (i.e. no residual tumour and negative histology margins) had an actuarial 5-year survival rate of 38 per cent, rising to 40 per cent if operative mortality is excluded (*Figure 2*), with 29 per cent or 31 per cent, respectively, considered tumour-free after that time. Twenty-five of the 80 patients undergoing hepatic resection before 1985 lived for more than 5 years, five of the 31 patients operated on before 1980 survived for 10 years, and the two who had been resected in the 1960s both lived for longer than 23 years with one still alive. Of the three patients who underwent hepatic resection in other hospitals, two died from recurrent disease after 14 and 66 months respectively, and one is alive without cancer relapse at 61 months.

For the potentially curative group the impact of various tumour-related and therapeutic features on prognosis is summarized in *Table 2*. With respect to crude actuarial survival, mesenteric lymph node involvement ($P=0{\cdot}0002$), synchronous detection of hepatic involvement ($P=0{\cdot}031$), presence of

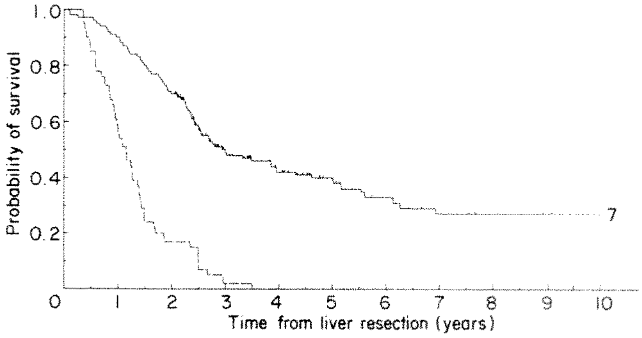

Figure 2 *Significance of extent of the procedure in patients resected with curative intent (group 3), excluding operative mortality.* ——, *Curative procedure* (n = *173*); ---, *non-radical procedure* (n = *41*). *The number at the end of the curve indicates the number of patients surviving beyond 10 years.* P < *0·00001*

Table 2 *Significance of various factors on survival and tumour-free survival following 'curative' hepatic resection, excluding operative deaths*

	No. of patients ($n=173$)	No. of 5-year survivors			Median length of survival (months)		5-year actuarial survival (%)	
		Crude survival	NED survival	Follow-up >5 years	Crude survival	NED survival	Crude survival	NED survival
Age								
<60 years	98	18	13	50	36	22	41	32
⩾60 years	75	7	7	30	32	20	36	30
Gender								
Male	94	16	12	46	39	20	41	29
Female	79	9	8	34	33	23	38	32
Primary tumour								
Colon	87	16	12	42	32	24	45	32
Rectum	86	9	8	38	33	18	33	29
Grading (Brothers)								
Grade 1/2	129	22	18	64	39	23	43	37
Grade 3/4	42	2	1	15	30	20	25*	13†
Mesenteric lymph nodes								
Not involved	49	14	14	26	73	44	53	50
Peripherally (C_1)	71	9	5	30	39	25	47§	29§
Centrally (C_2)	48	2	1	23	27	11	14	7
Liver metastases								
Synchronous	85	17	12	53	31	20	32	22
Metachronous	88	8	8	27	47	26	45†	39†
Number and distribution of metastases								
Solitary (± satellites)	105	18	14	53	33	21	40	30
Multiple unilateral	40	5	4	17	37	22	37	32
Multiple bilateral	28	2	2	10	33	17	39	35
Satellite metastases								
No	143	20	18	68	42	24	44	35
Yes	30	5	2	12	27	14	19‡	13†
Size of metastases								
⩽5 cm	125	17	13	58	46	25	42	33
>5 cm	48	8	7	22	29	13	34	24†
Type of resection								
Anatomical	125	14	11	45	39	26	42	34
Atypical	48	11	9	35	26	12	30	23*
Margin of clearance								
1–4 mm	67	11	8	39	30	14	28	23
5–9 mm	40	4	4	15	40	22	34†	29*
⩾10 mm	65	10	8	26	58	29	50	39
Year of resection								
1960–1979	31	12	9	31	29	20	40	29
1980–1987	142	13	11	49	36	22	39	31

NED survival, survival with no evidence of disease; * trend at $0{\cdot}05<P<0{\cdot}1$; † $P<0{\cdot}05$; ‡ $P<0{\cdot}01$; § $P<0{\cdot}001$

satellite metastases ($P = 0{\cdot}008$) and limited margins of clearance ($P = 0{\cdot}021$) were associated with a significantly worse outcome. Corresponding indicators of tumour-free survival were mesenteric lymph node involvement ($P = 0{\cdot}0005$), grading of the primary tumour ($P = 0{\cdot}028$), maximum diameter of the largest metastasis ($P = 0{\cdot}029$), presence of satellite nodules ($P = 0{\cdot}012$) and time of diagnosis ($P = 0{\cdot}047$). In contrast, multiplicity of metastases ($P = 0{\cdot}71/0{\cdot}69$) and a unilobar or bilobar distribution of multiple secondaries ($P = 0{\cdot}95/0{\cdot}57$) both failed to demonstrate a significant influence on survival and tumour-free survival, respectively (*Figure 3*).

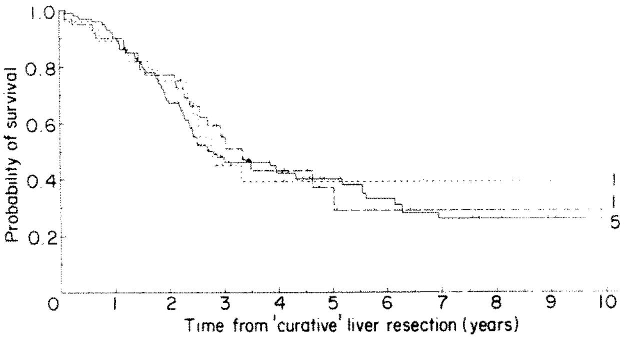

Figure 3 *Relationship between the number and distribution of metastases and survival after curative resection, excluding operative mortality (solitary metastases with satellite nodules are counted as solitary).* ——, *Solitary metastases* (n = *105*); – – –, *multiple metastases, unilateral* (n = *40*); -----, *multiple metastases, bilateral* (n = *28*). *The numbers at the ends of the curves indicate the number of patients surviving beyond 10 years.* P = *0·88*

Treatment failures after 'curative' resection

Of the 173 curatively resected patients who had survived surgery, 54 were alive at 1 January 1990 and ten had died with no evidence of recurrent disease. In three cases from the early 1970s the tumour status at death remained unclear (*Table 1*). The other 106 patients have developed definite cancer relapse which involved the liver in 74, the lungs in 50, the area of the primary growth in 16, and other areas in 34 cases. In 38 patients the initial relapse, and in 54 the known ultimate tumour distribution, appeared to be one of widespread multisystem failure.

We tried to analyse the possible impact of treatment in patients who had proven cancer relapse during follow-up. Survival was compared with that of group 2 patients (resectable disease confined to the liver that was just observed) and with procedures that were non-radical despite curative aim. Group 2 by definition did not involve patients with extrahepatic disease or more than three metastases. Although various other tumour-related factors were well matched among the three groups (*Table 3*), the survival rate was significantly superior in the 106 treatment failures following 'curative' procedures

Table 3 *Comparability of the three groups of patients analysed in* Figure 4

	Curative resection		Non-radical resection		No resection	
	No. of patients ($n = 106$)	%	No. of patients* ($n = 41$)	%	No. of patients* ($n = 59$)	%
Primary tumour site						
Rectum	52	49	21	51	28	47
Colon	54	51	20	49	31	53
Mesenteric lymph nodes						
Not involved	26	25	6	15	9	15
Peripherally (C_1)	44	41	14	34	19	32
Centrally (C_2)	34	32	17	41	29	49
Not classified	2	2	4	10	2	3
Grading of primary						
Grade 1/2	71	67	27	66	45	76
Grade 3/4	34	32	11	27	14	24
Not classified	1	1	3	7	–	–
Independent metastases						
Solitary (± satellites)	66	62	26	63	27	46
2 metastases	19	18	7	17	19	32
3 metastases	11	10	4	10	13	22
≥4 metastases	10	10	4	10	–	–
Satellite metastases						
No	84	79	37	90	58	98
Yes	22	21	4	10	1	2
Extrahepatic metastases						
No	99	93	36	88	59	100
Yes	7	7	5	12	–	–
Local recurrence						
No	99	93	37	90	59	100
Previously	1	1	1	2	–	–
Simultaneously	6	6	3	7	–	–
Time of diagnosis						
Synchronous	59	56	26	63	41	69
Metachronous	47	44	15	37	18	31
Maximum diameter (mm)						
Median (range)	42 (4–195)		34 (8–160)		40 (10–150)	
Percentage of hepatic involvement						
Median (range)	5 (1–75)		2 (1–35)		7 (1–60)	
Karnofsky index						
Median (range)	90 (60–100)		90 (40–100)		90 (40–100)	

* Operative deaths are excluded

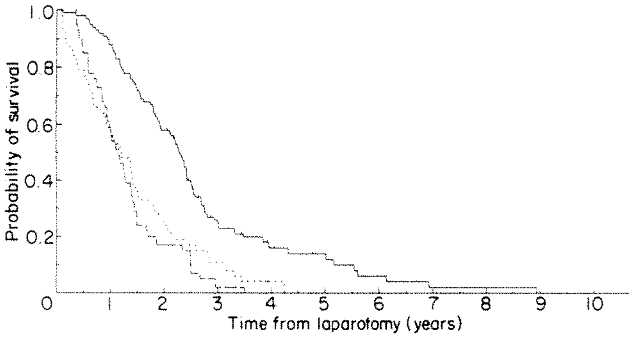

Figure 4 *Survival in patients with tumour recurrence following curative resection (——; n = 106) compared with group 3 patients with non-radical resection (– – –; n = 41) and group 2 patients having no resection (-----; n = 59), excluding operative mortality.* P < 0·0001

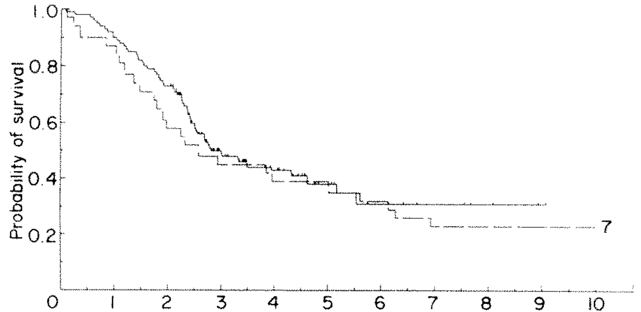

Figure 5 *Survival following curative resection in patients treated in the periods 1960–79 (– – –; n = 31) and 1980–87 (——; n = 142), excluding operative mortality. The number at the end of the curve indicates the number of patients surviving beyond 10 years.* P = 0·51

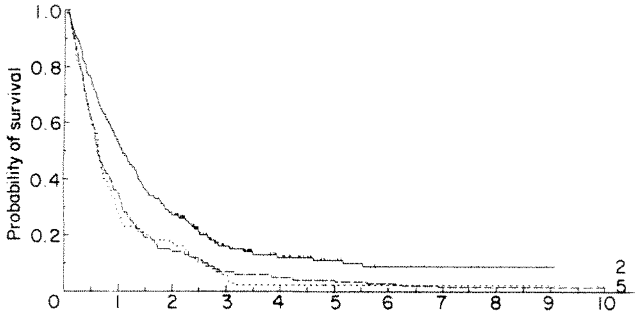

Figure 6 *Survival of the entire sets of patients undergoing laparotomy within the three decades, excluding operative mortality. ——, 1980–87 (n = 521); – – –, 1970–79 (n = 281); -----, 1960–69 (n = 90). The numbers at the ends of the curves indicate the number of patients surviving beyond 10 years.* P < 0·0001

($P < 0·0001$). It paralleled the results of the other two subsets with a shift forwards of nearly 12 months (median 27·3 months) and resulted in seven 5-year survivors and one patient who lived for almost 9 years (*Figure 4*).

Prognosis by period of time

The proportion of patients who underwent curative resection increased from 2 per cent in the 1960s and 9·5 per cent in the 1970s to 20·5 per cent in the 1980s. This indicates an expanding surgical approach since 1980, but the survival figures following curative resection have not changed (*Table 2, Figure 5*). The 5-year survival rate was 39 per cent in the 142 patients who had curative resections performed in the 1980s, compared with 40 per cent in 31 patients having curative resections in the 1960s and 1970s (13 and 12 5-year survivors in the two groups).

If in turn patients undergoing laparotomy within the three decades are analysed irrespective of treatment, 3-year and 5-year survival rates were 6 and 2 per cent in the 1960s, 7 and 3 per cent in the 1970s, and 16 and 11 per cent for patients seen from 1980 onwards, respectively (*Figure 6*).

Discussion

It is obvious that biological behaviour prevails over surgical enthusiasm in deciding the fate of patients with colorectal liver metastases[16]. However, we have to distinguish between the limited impact of aggressive surgery upon the entire sample of patients suffering from metastatic spread and the possible advantage that may be offered to a subgroup with completely resectable disease[17]. To judge the significance of hepatic resection in these patients requires a basic consensus as to which criterion is most reliable for this assessment. Some authors rely on median survival figures or median tumour-free survival[10,14]. In almost all series the majority of patients undergoing hepatic resection finally die from cancer relapse, and median survival time therefore illustrates the speed of failure rather than serving as a measure of the ultimate success of treatment. Long-term results, as judged by a period of survival which cannot be expected from the natural history, would provide a better criterion.

Five-year survival rates seem to comply with those conditions[18,19]. Analysing very cautiously the fate of 1650 untreated patients in the English language literature from 1952 onward, Hughes and co-workers collected only 14 patients who had survived for 5 years. In just four of them the diagnosis had been confirmed histologically. Little is known about the maximum length of survival in these patients, but all finally died from intrahepatic tumour progression[20].

In our series there were no 5-year survivors among 960 surgically untreated patients, 23 who underwent deliberate debulking, and 43 cases with non-radical resection. This may predominantly reflect an advanced stage of intrahepatic and, in about 40 per cent of cases, extrahepatic disease. However, this sample contains a small subgroup of 62 patients suffering from metastases confined to the liver who were suitable for resection by current criteria but who were only observed because of a formerly conservative approach to hepatic resection. It also involves 34 patients with all gross tumour removed, but with positive margins. Here the lack of long-term success surely strengthens the case for adequate surgical intervention.

If long-term success was deemed to reflect case selection only, then one would expect the three decades studied to reflect the different therapeutic attidues in a particular way. Some untreated long-term survival should occur in the earlier periods, because during the 1960s resection of secondary tumours was not a popular option. Only four highly selected patients underwent excision of easily accessible solitary metastases. Two of them survived for more than 20 years, and one is still alive with no evidence of disease. The other two had positive margins and illustrate the common tendency to underestimate the intrahepatic tumour extent during minor wedge excisions[21,22]. They died 11 and 29 months after operation from recurrent liver disease. During this first decade 12 additional patients presented with what appeared to be a solitary hepatic metastasis. A further ten showed two or three nodules, which were restricted to one half of the liver in seven cases. Sixteen of these 22 patients were free from extrahepatic disease and would today be clear candidates for hepatic resection. Only two lived for 3 years and none survived for 4 years.

The second decade was characterized by positive feedback that indicated some long-lasting success following surgical resection of secondaries from both the liver and lungs[23]. The interest in this mode of treatment therefore increased. As in the Mayo Clinic experience[3], resection was progressively extended to include multiple and bilateral secondaries, but 34 resectable patients remained untreated. None of them survived for 5 years.

Due to the absence of an effective therapeutic alternative and the growing experience in hepatic resection, indications were extended during the 1980s to include virtually all patients with lesions that were technically resectable. There was almost no age limit. The oldest patient resected for cure was aged 91 years, and the oldest undergoing a formal right hepatectomy was 80 years old at the time of surgery. Cases with up to seven individual lesions, metastases accompanied by several satellite nodules, and seven patients presenting with additional pulmonary deposits are included in the group classified as curative. Despite this increasingly aggressive surgical approach, survival figures following curative procedures have not changed when compared with the results obtained during the 1960s and 1970s. If, in turn, prognosis is estimated with no regard to the treatment actually performed, there is a significant improvement for the entire sample of patients undergoing laparotomy from 1980 onwards.

The better results obtained more recently may to some extent be due to increasing diagnostic sensitivity[24]. This is reflected in recent debate as to the 'true' age of metastases previously detected at operation. A lead time bonus of 3·7 years, derived from cell kinetic calculation[25], has been claimed. Reported 2-year survival figures of 20 per cent were projected as the true 5-year survival standard, and reported 5-year survival figures were stated as the true 9-year survival rate[15]. There is, no doubt, a zero time shift in more recent experience which may explain a small proportion of untreated 5-year survival in series to come, as reflected in our three untreated patients alive in the fifth year. However, projection of these estimates on former retrospective data does not contribute to a more accurate interpretation. A similar time bonus would be due to patients having previously undergone resection as well, because they did not differ significantly in respect of tumour size and extent from matched untreated historical controls[16].

Focusing on the subgroup undergoing potentially curative resection, our results not only show a reasonable proportion of patients achieving long-term survival but also challenge the common assumption that only the 25–30 per cent of patients who survive 5 years without recurrent disease benefit from hepatic resection[26]. This is for two reasons. Patients who were symptomatic from advanced hepatic involvement were usually palliated for months or even years by removal of their intrahepatic masses. Although they finally succumbed, they represent therapeutic success as mentioned by Adson[18]. Second, survival was prolonged even by an ultimately unsuccessful resection, if it was initially 'curative'. The 106 patients who eventually developed cancer relapse despite complete removal of their metastases demonstrated significant superiority when compared with similar patients who underwent resection with positive margins, or patients in whom no treatment was offered despite resectable metastases confined to the liver. Factors of proven or supposed influence on prognosis, such as mesenteric lymph node involvement or number and distribution of hepatic metastases, were well matched within these three groups. Whereas non-radical resection neither modified the prognosis of untreated patients nor led to any 5-year survival, curative procedures, even though finally unsuccessful, resulted in a shift forward of 1 year or so and an increase in longevity of up to 8 years.

Is it any longer ethical to assign patients to a prospective randomized trial when surgical resection has become so safe and the evidence of prolonged survival is so overwhelming? Would any patient, having been advised of all the facts, risk losing the only chance of cure? For those with little experience of aggressive surgery for this condition, a trial of hepatic resection against chemotherapy might be an attractive proposition. However, disease-free survival of more than 20 years was observed twice in our series and is also reported by Adson[27] and Butler *et al.*[28]. From such results we feel that resection for attempted cure should be offered to all suitable patients until such time as any other form of treatment can be shown to offer similar benefits.

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Extended hepatectomy for hepatocellular carcinoma

The results of extended hepatectomy in 25 patients with hepatocellular carcinoma performed over a 16 year period have been reviewed, analysed and compared with those of 144 patients who underwent lesser liver resection. Five left and 20 right extended hepatectomies were performed for tumours ranging from 3 to 20 cm in diameter. Seventeen (68 per cent) of the patients had non-cirrhotic livers. The major postoperative complications were: haemorrhage in five cases, major bile duct injury in three, subphrenic abscess in two, liver failure in one and wound dehiscence in one. The 30-day (operative) mortality rate was 12 per cent and the median survival duration, including operative mortality, was 9·7 (range 0·2–32·1) months. The survival rate was 46 per cent at 1 year, 33 per cent at 2 years and 22 per cent at 3 years. The morbidity, mortality and survival data of extended hepatectomy were comparable with the results of lesser hepatic resections for hepatocellular carcinoma. We conclude that extended hepatectomy is a worthwhile operation for large hepatocellular carcinomas and a viable alternative to liver transplantation.

Keywords: Hepatocellular carcinoma, surgery, liver resection

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Hepatic resection is the only treatment option that may allow putative cure for hepatocellular carcinoma[1]. During the last 30 years hepatic resection has been increasingly undertaken for this condition, probably because surgeons have developed a better understanding of liver anatomy and physiology. However, the use of extended hepatic resection for large hepatocellular cancer remains controversial because of the poor related prognosis and the condition of the patients, who usually present with their disease at an advantaged stage. Although no study has been performed on the use of extended hepatectomy for hepatocellular cancer, it is generally assumed that, compared with hemihepatectomy or segmentectomy, this operation carries higher morbidity and mortality rates[2]. One of the arguments against extended hepatectomy is that, because the tumours requiring such resections are usually large and extensive, the resection margins are often inadequate[3]. Large tumours also have high incidences of vascular invasion and metastasis[4,5]. These factors are associated with early tumour recurrence and short survival. It is the opinion of some surgeons that large liver tumours should be treated by liver transplantation, particularly in younger patients[6], and if this is not possible non-operative or supportive treatment alone should be instituted.

We have reviewed our experence of extended hepatectomy for hepatocellular cancer. The results have been analysed and compared with those of less radical liver resection.

Patients and methods

The clinical records of all patients undergoing resection for hepatocellular cancer at the Department of Surgery, University of Hong Kong, at Queen Mary Hospital between 1972 and 1987 were reviewed. During the study period, peritoneoscopy was performed on all patients before operation to assess the extent of the tumour, the presence of cirrhosis and degree of hypertrophy or shrinkage of different parts of the liver. Liver biopsy was performed during peritoneoscopy under direct vision. The procedure of extended hepatectomy was then chosen in appropriate patients, based mainly on size, extent and location of the tumour (see below).

The anatomical division of the liver into segments as described by Couinaud[7] was adopted. Cantlie's line was regarded as the line of demarcation between the right and left lobes of the liver. Left extended hepatectomy was defined as the resection of the left lobe (segments II, III and IV) in continuity with segment VIII and all or part of segment V. Right extended hepatectomy was the resection of the right lobe (segments V, VI, VII and VIII) in continuity with segment IV.

Extended hepatectomy was performed for tumours which involved or extended beyond Cantlie's line. These were usually large tumours, sometimes replacing one lobe of the liver. However, extended hepatectomy was also performed for smaller tumours located in segments IV or VIII, or straddling Cantlie's line in non-cirrhotic patients. In cirrhotic patients, the line of resection was tailored to obtain a good margin beyond the tumour edge while trying to conserve as much of the unaffected liver as possible to prevent postoperative liver failure. Regardless of whether cirrhosis was present, only patients without ascites or jaundice, and having a normal or near normal clotting profile, were selected for extended hepatectomy.

During each operation preliminary vascular control was obtained before resection by dividing the vessels at the hilum. The hepatic veins were also divided or ligated, whenever possible, before transecting the liver parenchyma. The right hepatic vein was exposed by mobilization and rotation of the right lobe anteriorly and medially. The left hepatic vein was approached by rotating and depressing the left lobe inferiorly.

The transection of liver parenchyma was performed using a combination of finger fracture and forceps crushing techniques. Pringle's manoeuvre was performed before transection of liver parenchyma in all cases. The common bile duct was not splinted except when injury to the bile duct was recognized and repaired at the time of surgery.

The Kaplan–Meier method was used to calculate survival[8]. Comparison of survival of the extended hepatectomy and non-extended hepatectomy groups was done using the generalized Kruskal–Wallis test as suggested by Breslow[9].

Results

During the 16-year study period a total of 1383 patients with hepatocellular cancer were referred to the Department of Surgery and 169 (12·2 per cent) had resection of the tumour. None of the patients in the resection group had a tumour classified as a fibrolamellar variant of hepatocellular cancer. Of the patients undergoing liver resection 111 (65·7 per cent) also had histologically proven liver cirrhosis.

Extended hepatectomy was performed on 25 patients (15 per cent). The age of the patients ranged from 29 to 72 years (median 53 years) and they included four women and 21 men. Sixteen patients (64 per cent) had an elevated serum α-fetoprotein level (normal <20 ng/ml). Hepatitis B virus surface antigen status (HbsAg) was positive in 12 patients

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Table 1 *Complications after extended hepatectomy and hepatectomy of a lesser extent*

Complication	Hepatectomy of a lesser extent* ($n = 144$)	Extended hepatectomy ($n = 25$)
Haemorrhage	18 (12·5)	5 (20)
Liver failure	18 (12·5)	1 (4)
Subphrenic abscess	11 (7·6)	2 (8)
Wound infection	12 (8·3)	2 (8)
Pneumonia	7 (4·9)	1 (4)
Haematoma	4 (2·8)	1 (4)
Bile duct damage	3 (2·1)	3 (12)
Gastrointestinal bleeding†	4 (2·8)	0
Other complications	8 (5·6)	0

Values in parentheses are percentages. * Some patients have more than one complication. † Not included four patients with variceal bleeding who are included in the liver failure category

(48 per cent) and eight (32 per cent) had histologically proven liver cirrhosis. The median tumour diameter was 12 cm (range 3–20 cm). Five patients underwent extended left hepatectomy and 20 underwent extended right hepatectomy. The tumour ruptured in two patients during operation. One patient had an additional right hemicolectomy and two patients had partial resection of the right hemidiaphragm because of tumour invasion.

Of the 144 patients undergoing lesser liver resections, 124 were men and 20 were women. Their ages ranged from 24 to 79 years (median 54 years), 83 per cent had an elevated serum α-fetoprotein level, 81 per cent had positive HbsAg status and 64 per cent had liver cirrhosis. The median tumour diameter was 8 cm (range 1–25 cm). The types of hepatectomy performed were right hemihepatectomy in 65 patients, left hemihepatectomy in 34 patients, lateral segmentectomy in 13 patients and partial hepatectomy in 32 patients.

Fifteen complications occurred in 11 of the patients undergoing extended hepatectomy (*Table 1*). Liver failure was defined as the occurrence of ascites, variceal haemorrhage, hepatic encephalopathy occurring after operation and jaundice (bilirubin $> 50\ \mu$mol/l) which persisted beyond 2 weeks after operation. Seven patients underwent re-exploration for postoperative haemorrhage (five patients), left hepatic duct stricture (one patient) or wound dehiscence (one patient). The operative mortality, defined as death within 30 days of operation, was 12·0 per cent. The 60-day mortality rate was also 12·0 per cent.

The operative mortality (13·9 per cent), 60-day mortality (16·7 per cent) and morbidity (48·6 per cent) rates of patients undergoing lesser liver resections were similar. The types of complications of the two groups are compared in *Table 1*. Patients undergoing extended hepatectomy had a proportionally higher incidence of postoperative haemorrhage and bile duct injury. The incidence of liver failure, anticipated to be higher in the extended hepatectomy group, was actually lower. This could be attributed to the lower incidence of cirrhosis in the extended hepatectomy group and careful patient selection. Nevertheless, none of the eight cirrhotic patients undergoing extended hepatectomy suffered liver failure, showing that this procedure can be performed in carefully selected cirrhotic patients without producing liver failure.

The survival rate of patients undergoing extended hepatectomy, inclusive of operative mortality, was 46 per cent at 1 year and 22 per cent at 3 years. The median survival duration was 9·7 months. Three patients survived more than 5 years and two patients survived more than 10 years; all five patients are still alive. There was no statistically significant difference in survival between patients undergoing extended hepatectomy and those undergoing hepatectomy of a lesser extent (*Figure 1*). For the latter group, the 1, 3 and 5 year survival rates were 45, 21 and 14 per cent respectively. The median survival duration was 9·9 months. Fourteen patients survived for more than 5 years (10 still alive) and six patients survived for more than 10 years (all still alive).

Discussion

Hepatocellular cancer is one of the most common fatal malignancies in the world[10]. Improvement in diagnostic techniques and better understanding of the surgical anatomy and physiology of the liver may now offer the chance of intervention at an earlier stage with a better prospect of cure. Hong Kong has a high incidence of this cancer[11] but the patients usually present late when their tumour has already enlarged to a substantial size and often beyond the scope of surgery[12,13]. Some patients have tumours which are clearly amenable to surgery but in others, because of the size, extent and location of the tumours, the possibility of resection is less clear-cut as only extended hepatectomy can offer clearance by resection.

About 70 per cent of patients with hepatocellular cancer in Hong Kong and in other areas of high incidence have liver cirrhosis[14–17]. One cause of reluctance to perform major hepatic resection in cirrhotic patients is that liver failure may occur as the result of loss of functioning parenchyma[18–23]. Our study shows that by adhering to clinical assessment, as outlined above, the chance of postoperative liver failure is low. The incidence of liver failure in our series of patients was actually higher in patients undergoing hepatectomy of a lesser extent, suggesting that the occurrence of liver failure was not related to the anatomical extent of liver resection, and was more probably related to the functional capacity and volume of the remaining liver. The cirrhotic patients in this study undergoing extended hepatectomy had large tumours replacing most of the affected liver lobe. Removing a lobe resulted in minimal loss of functioning parenchyma as the uninvolved part of the liver was often hypertrophied.

Impairment of liver function can be assessed by dye clearance tests. Okamoto *et al.*[24] have devised a formula to estimate the risk of liver failure in cirrhotic patients undergoing resection which takes into account the liver function impairment, as measured by the indocyanine green clearance test, and the estimated volume of remaining liver. While this is a logical method to predict mortality or liver failure in cirrhotic patients, the method remains to be substantiated. We have used bromsulphthalein clearance tests in the past and more recently indocyanine green clearance tests to estimate liver function. The cut-off points of these tests, above which resection would not be performed, has been continuously revised upwards as more operative experience has accumulated.

Previously, in non-cirrhotic patients, we have performed extended hepatectomy for smaller tumours of 5 cm diameter

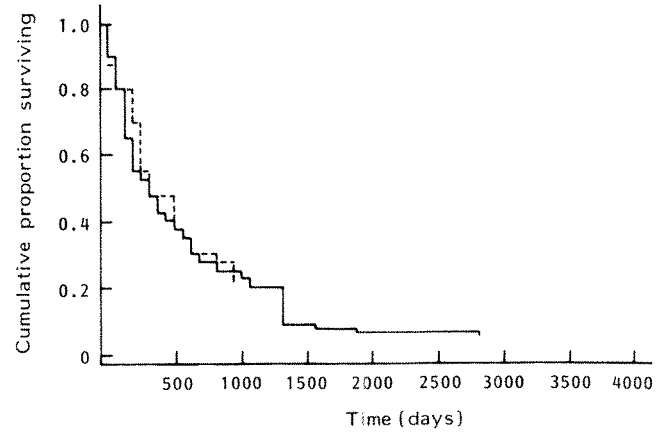

Figure 1 *Survival as assessed by life table analysis after extended (– – –) or lesser extents (——) of hepatectomy for hepatocellular cancer*

or less, situated in segments IV or VIII or straddling Cantlie's line. This was done to obtain maximal tumour clearance and to minimize the amount of tissue remaining which might bear tumour. We have ceased this practice in favour of segmental resection in recent years.

This study shows that extended hepatectomy may be associated with a higher incidence of bile duct damage and postoperative haemorrhage. Starzl and colleagues[2,25] reported that three of their first four patients who had an extended left hepatectomy suffered biliary complications. We found that bile duct damage could occur even if the surgeon was experienced because the normal relationship of structures may be grossly distorted by the large tumour and by the hypertrophy of certain parts of the liver. One other factor may be that the hepatic ducts were dissected and exposed for a considerable length and therefore devascularized. Damage may thus occur during the dissection or after operation because of ischaemia. For tumours of the left lobe located close to the diaphragm, we have tried to preserve part of segment V during extended left hepatectomy to prevent damage to the right hepatic duct.

The source of bleeding in three of the five patients who had postoperative haemorrhage was the thoracotomy incision used in the thoracoabdominal approach. Bleeding was from the cut edge of the diaphragm in two patients and from an intercostal artery in one. The diaphragm was often very vascular in these patients because of collateral blood supply to the tumour and associated portal hypertension. The bilateral subcostal incision was used more frequently in the latter part of the study and we have found that extended hepatectomy can be performed through this incision in the majority of patients. Only very large tumours located in the dome of the right lobe may require thoracoabdominal incisions. Both intraoperative and postoperative haemorrhage were less frequent when the chest was not opened. Postoperative haemorrhage also occurred from the cut surface of the liver, damaged adrenal veins, raw surfaces of the diaphragm and posterior peritoneum. Some of the bleeding consisted of a generalized ooze from raw surfaces which did not stop unless the blood clot was evacuated by re-exploration. This form of postoperative haemorrhage may be avoided by better drainage systems which prevent accumulation of blood clots. Arrest of bleeding from raw surfaces and from the liver edge can be obtained by suture plication. We have found that topical thrombin is also quite effective in haemostasis of these surfaces, particularly when overlaid by a piece of oxidized cellulose.

Extended hepatectomy was mainly undertaken for large tumours and, as shown by this study, the results were by no means outstanding. The results of liver transplantation have steadily improved in recent years and transplantation may offer an alternative method of treatment[26,27]. For multinodular or multicentre tumours which are scattered throughout but still confined to the liver, total excision is possible only via liver transplantation. Liver transplantation is also an alternative procedure for large tumours, the removal of which requires extended liver resection. Soreide *et al.*[28] advocated resection for large tumours and the results were especially favourable for the fibrolamellar variant of hepatocellular carcinoma. In our study the operative mortality and survival after extended hepatectomy and after hepatectomy of a lesser extent were similar, which we feel justifies the continued performance of extended hepatectomy for large tumours.

The long-term results of liver transplantation for hepatocellular cancer are starting to emerge. Iwatsuki *et al.* reported 1 and 3 year actuarial survival rates of 68 and 43 per cent respectively[29]. These results are better than those reported in our study. However, few patients with smaller lesions and lesions incidentally discovered while transplanting cirrhotic livers were included. It is likely that if such tumours are excluded the results would be comparable to those achieved by extended hepatectomy. Williams and O'Grady[30] reported that 74 per cent of 50 patients with hepatocellular cancer undergoing liver transplantation survived for >3 months and that 65 per cent of patients surviving had evidence of recurrence. Thus, the survival rate may not improve with liver transplantation. The role of liver transplantation needs further evaluation but, currently, it should be reserved for patients with scattered nodules in both lobes of the liver which cannot be encompassed by extended hepatectomy.

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Case report

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Antigen CA 19-9 and mucinous cystadenoma of the pancreas

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Cystadenomas of the pancreas are rare but well recognized entities. Serous cystadenomas are always benign whereas mucinous cystic neoplasms can become malignant and must be excised. We report a case of mucinous cystadenoma which was benign but recurred 1 year after resection. A rise in the level of carbohydrate antigen CA 19-9 preceded the recurrence.

Case report

A 41-year-old woman presented with a 3-month history of epigastric pain. On abdominal examination there was no tenderness or mass. Barium meal suggested a retrogastric mass and ultrasonography revealed a large thick-walled cyst (7 cm) of the tail of the pancreas. A computed tomography scan confirmed the presence of the cyst and showed intraluminal papillary projections. Endoscopic retrograde cholangiopancreatography (ERCP) showed a communication between the cyst and an otherwise normal pancreatic duct (*Figure 1*). Serum CA 19-9 level (Oris ELSA CA 19-9, Oris Industries, Gif sur Yvette, France) was very high at 1130 units/ml (normal <37).

At laparotomy (January 1988) the cyst was located on the pancreatic tail, the remaining part of the organ appearing normal. A distal pancreatectomy and splenectomy was performed. Macroscopic examination revealed a cyst 8 × 6 cm in size with mucinous content surrounded by a fibrous wall. Numerous small cysts filled with mucoid fluid were found along the internal surface in the fibrous wall. Histologically, the cystic spaces were lined by a single layer of mucin-producing columnar cells. Neither cellular atypia nor mitosis were noted. Immunohistochemical staining for CA 19-9 was strongly positive in the epithelial lining of the cyst (*Figure 2*). The patient made an uneventful recovery. Ten days after excision of the neoplasm the CA 19-9 level decreased to 119·4 units/ml. The patient was well for 1 year. However, the CA 19-9 level still remained high at around 100 units/ml (*Figure 3*). One year later ultrasound examination and a computed tomography scan demonstrated tumour recurrence near the pancreatic stump. At a second laparotomy (January 1989) further resection of both the pancreas and the whole tumour was carried out. The gross appearance was of a 7 × 5·5 cm large multicystic tumour. Histological examination showed similar features to those of the first tumour without evidence of malignancy. Six months later serum CA 19-9 level is normal (32 units/ml) and the patient is well.

Discussion

Mucinous cystic pancreatic neoplasms can be benign or

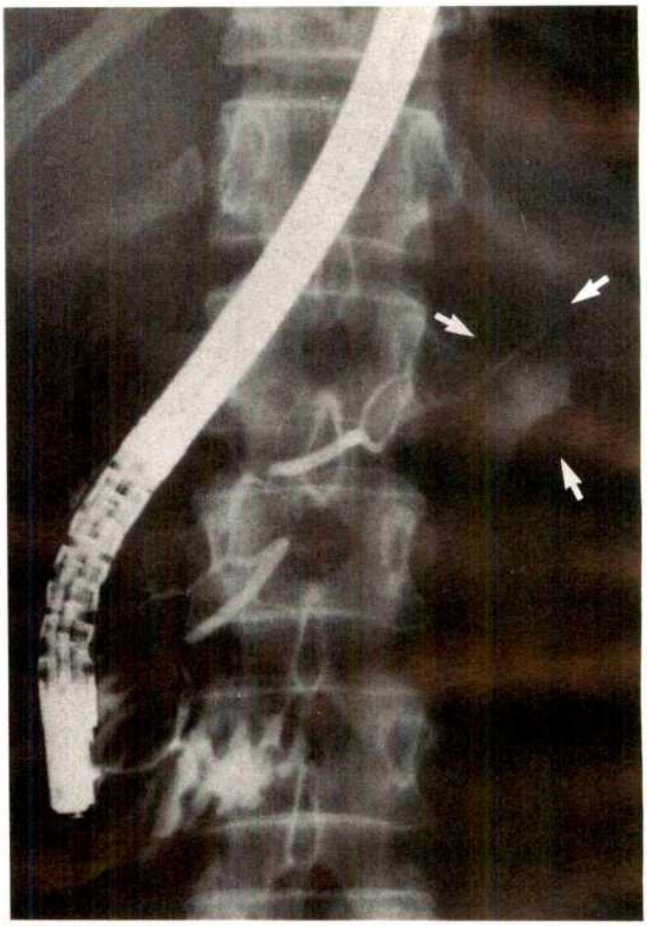

Figure 1 *ERCP showing communication between pancreatic duct and cyst (arrowed)*

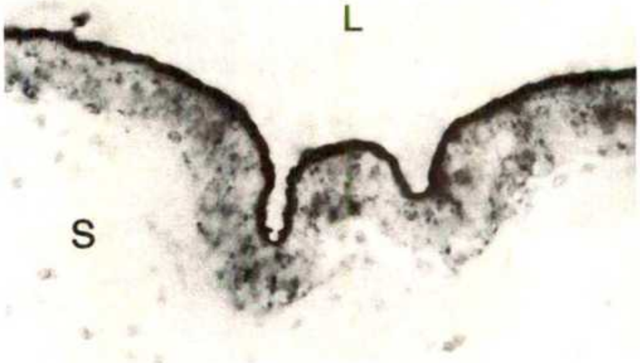

Figure 2 *Strong apical CA 19-9 immunostaining. Lumen, L; stroma, S. (Immunoperoxidase, original magnification × 120)*

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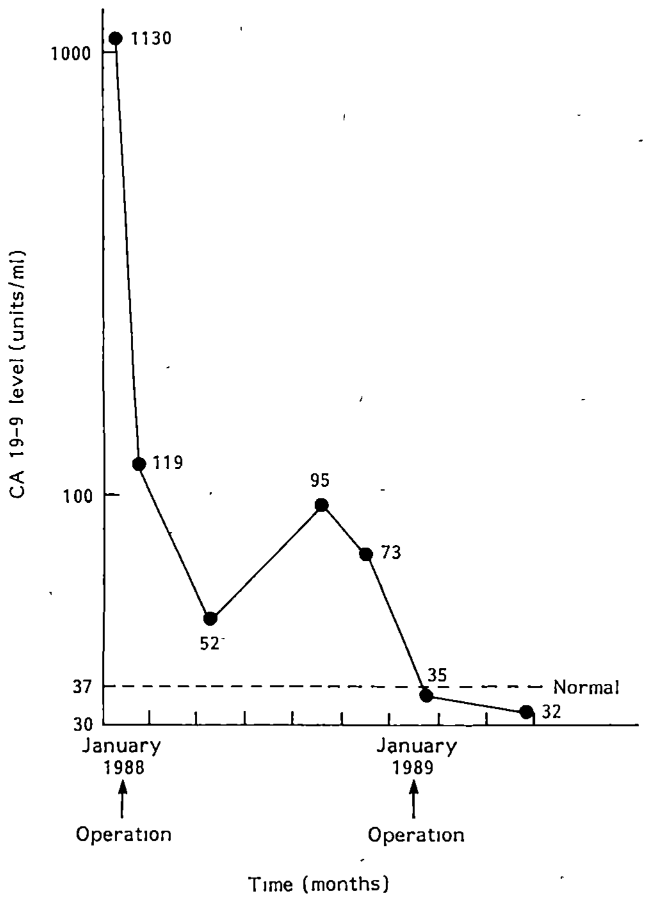

Figure 3 *Serum level of CA 19-9*

malignant (cystadenocarcinomas), but, as the distinction is not always clearcut, Compagno and Oertel[1] called them 'mucinous cystic neoplasms with overt or latent malignancy'. Our patient presented with a typical mucinous cystadenoma although ERCP demonstrated communication between the cyst and pancreatic duct[2]. Histological examination of the whole tumour removed at the first laparotomy revealed neither carcinoma nor cellular atypia. Although the entire tumour seemed to have been resected, recurrence appeared within 1 year. Examination of the recurrent tumour after total excision did not show malignancy. In this circumstance serum CA 19-9 level was a good marker of the recurrence.

All authors agree that a mucinous cystadenoma can become malignant; however, there have been no reports of such lesions which have been totally excised in which malignancy was missed or at least suspected[1,3–7]. False diagnosis, i.e. mucinous cystadenoma judged to be benign but with subsequent malignant change, has been observed only when the tumour was biopsied and not completely removed. This situation was particularly frequent when these lesions were treated as pseudocysts and simply drained[5]. In Compagno and Oertel's[1] series of 41 mucinous cystadenomas fourteen were malignant, 10 presented with cellular atypia and 17 were benign. Twelve patients died from metastases, including two cases with cellular atypia and one where the lesion was judged to be benign on the basis of biopsy alone. Hodgkinson *et al.*[3] reviewed 45 pancreatic cystadenomas treated surgically in the Mayo Clinic between 1939 and 1975, and found no recurrence in 31 patients who had total removal of their tumour. Von Segesser and Rohner[4] also failed to observe recurrence after curative resection with a maximum follow-up of 22 years. Yamaguchi and Enjoji[6] observed 11 patients: five had malignant tumours, four had benign lesions and two had lesions which were judged to be borderline in view of severe atypical epithelium focally but without further evidence of malignancy. One patient with malignancy died 3 months after surgical removal of the tumour, the remaining 10 patients are well 2–57 months after surgery with no signs of recurrence or metastasis. In 11 cystadenocarcinomas observed in 20 years, ReMine *et al.*[7] divided the patients into two groups. Those with a high grade of malignancy showed obvious malignancy with metastases and short survival; of those with low grade malignancy, only two of five recurred after surgical removal of the tumour. We conclude that our first resection missed microscopic areas of mucinous cystic neoplasm even if no evidence of incomplete resection was noted on the specimen.

CA 19-9, defined as a monoclonal antibody which recognizes a sialylated form of Lewis antigen, is present in normal pancreatic tissue, meconium and normal gallbladder. Its specificity in the screening of pancreatic cancer is controversial. A moderately increased concentration has been noted in benign pancreatic disease, especially in jaundiced patients. In such cases CA 19-9 levels are correlated with alkaline phosphatase levels. Tatsuta *et al.*[8] studied serum CA 19-9 level in 17 patients with pancreatic cysts and found a great overlap between the values in patients with malignant cysts and those with benign cysts (including pseudocysts). Serum concentration of CA 19-9 is correlated with the size of pancreatic tumour and with lymph node involvement. Our patient showed a very high level of CA 19-9 (1130 units/ml) with evidence of neither malignancy nor retention. Immunohistochemical staining was positive for the antigen. Haglund *et al.*[9] also found intense staining in mucinous cystadenomas and explained this fact by the ductal origin of these tumours in contrast to the serous cystadenomas in which no expression of CA 19-9 was demonstrated. Yamaguchi *et al.*[6] found a slight difference in the immunohistochemical location of CA 19-9 in malignant mucinous cystadenocarcinomas compared with that in benign or borderline lesions; in cases of malignancy, CA 19-9 staining appeared diffuse in cytoplasm and/or stroma whereas in benign conditions only granular cytoplasm exhibited fixation of CA 19-9.

In conclusion, our case highlights two points: first, mucinous cystadenoma judged benign in the light of histological findings may recur locally after resection which appears complete from the surgical and histological point of view; second, in this instance CA 19-9 serum level may prove to be a marker of value in the detection of recurrence.

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Effective intraperitoneal antiprotease therapy for taurocholate-induced pancreatitis in rats

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In canine pancreatitis, irreversible hypotension and death follow saturation of the antiprotease molecules in peritoneal exudate by activated proteolytic enzymes which are released from the pancreas. This study has examined, in rats with taurocholate-induced pancreatitis, the efficacy of removal of the peritoneal exudate by aspiration and a single lavage, followed by instillation of an exogenous antiprotease solution. Instillation of human fresh frozen plasma, containing α_2-macroglobulin and α_1-antiprotease, was associated with the longest median survival. Aprotinin, although possessing a much greater trypsin inhibitory capacity, just failed to significantly improve the median survival time compared with the control group. Intraperitoneal antiprotease therapy is simple to perform, has a beneficial effect on survival time in this model and merits investigation in man.

Keywords: Acute pancreatitis, intraperitoneal antiprotease therapy

Typically two phases of mortality are recognized in acute pancreatitis Death may occur early, within the first week, often from a 'shock-like' illness complicated by respiratory, cardiovascular and renal failure. Patients surviving this phase may succumb later due to the local effects of pancreatic necrosis and sepsis. Trapnell found that 45 (59 per cent) of his patients died early, 33 within the first 48 h[1]. The majority (67 per cent) had oedematous pancreatitis at post mortem[1], a seemingly mild, recoverable pancreatic lesion. 'Toxic factors', which are released into the circulation from the inflamed pancreas[2] or from the commonly associated peritoneal exudate[3–5], are probably responsible for this early shock-like illness.

Proteolytic enzyme activity has been demonstrated in the peritoneal exudate of dogs with pancreatitis induced by the closed duodenal loop technique[6] and by retrograde intraductal injection of bile[7]. Overwhelming the peritoneal antiproteases by activated proteolytic enzymes was associated with the onset of irreversible hypotension and subsequent death of the animals[6]. Toxic effects may result from the intraperitoneal activation of zymogens and the complement and kinin systems, with release of small vasoactive peptides, including histamine, which cross the peritoneum to exert a systemic effect.

This study has investigated the adequacy of the peritoneal antiprotease defences in rats with taurocholate-induced pancreatitis and the therapeutic efficacy of a novel treatment comprising removal of the exudate followed by instillation of an antiprotease solution.

Materials and methods

Induction of pancreatitis

Pancreatitis was induced in fasted, male Wistar rats by the controlled, retrograde, intraductal infusion of sodium taurocholate (freshly prepared in 0 9 per cent saline solution). Initial reports of this technique had described a 'free hand' injection of bile salt solution[8,9] which would be expected to produce variability in the pressures generated and degree of pancreatic injury. A pilot study showed that sodium taurocholate 5 per cent, 0·6 ml infused at 200 μl/min, produced a consistently high mortality rate (83 per cent within 24 h)

Before closure of the abdomen a peritoneal dialysis cannula was placed adjacent to the pancreas. Only after successful completion of the procedure were the animals randomly allocated to one of four groups receiving intraperitoneal therapy or to a control group, the randomization ensuring five groups each of ten rats.

Experimental protocol

In rats randomized to receive intraperitoneal therapy the peritoneal cavity was aspirated 1 h after the induction of pancreatitis and then lavaged with 0·9 per cent saline solution (1·5 ml/100 g body-weight). The lavage fluid was aspirated and finally the test solution was instilled (1·5 ml/100 g body-weight) before withdrawal of the dialysis cannula. Active antiprotease or inactive solutions were studied as follows: aprotinin 5000 kallikrein inactivator units/ml in 0·9 per cent saline solution (Trasylol®, Bayer, FRG), 0 9 per cent saline solution, human fresh frozen plasma (whole plasma containing clotting factors and the natural antiproteases including α_2-macroglobulin and α_1-antiprotease; Glasgow and West of Scotland Blood Transfusion Service, Law Hospital, Carluke, UK) or human plasma protein solution (a colloid solution, predominantly of albumin at a concentration of 45 g/l, devoid of antiproteases and other active plasma factors; Scottish National Blood Transfusion Service Protein Fractionation Centre, Edinburgh, UK)

In the control group 0 9 per cent saline solution was injected subcutaneously (1 5 ml/100 g body-weight) 1 h after the induction of pancreatitis and the peritoneal cannula withdrawn without removing any exudate.

After surgery the rats were permitted free access to water, food pellets being reintroduced 24 h later The animals were examined hourly and the time of death recorded Animals surviving to 72 h were killed. Post mortem examination was performed immediately after death on all animals. The extent of the pancreatitis in the head and tail of the gland was graded macroscopically on a scale 1–4, corresponding to a normal appearance, mild inflammation/thickening, severe inflammation/thickening or necrosis respectively. The extent of fat necrosis in the peritoneal cavity was recorded as none, localized to the pancreas, regional or generalized. The pancreas was excised and the pancreatic weight recorded The pancreas was then fixed in formalin, processed, sectioned and stained with haematoxylin and eosin for histological examination.

Biochemical analyses

The volume and colour[10] of the exudates and lavage fluids aspirated from the peritoneal cavity were recorded 1 h after the induction of pancreatitis in the intraperitoneal therapy groups and in all groups at post mortem examination. The exudates were centrifuged and the supernatants stored at −20°C. The exudates were subsequently examined for evidence of free proteolytic activity, its presence indicating overwhelming of the peritoneal antiprotease defences. The specimens were thawed at room temperature and 20 μl aliquots were applied to a 0·2 per cent fibrin plate[11], prepared from plasminogen-free fibrinogen (Poviet B V., Organon Tecknica, Cambridge, UK). Free proteolytic activity was judged to be present if fibrinolysis appeared following

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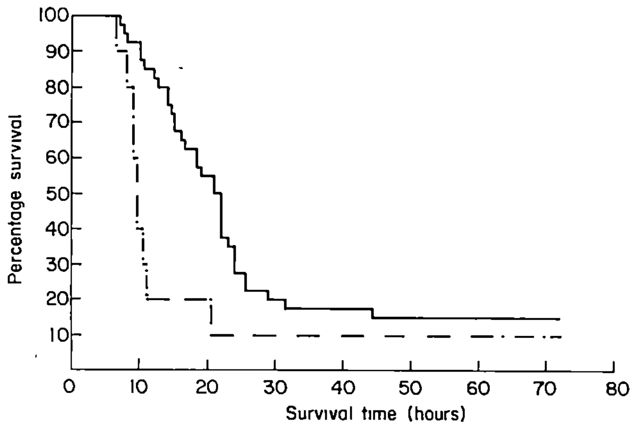

Figure 1 *Life table showing improved survival amongst the 40 rats randomized to receive intraperitoneal therapy (——) compared with the ten controls (–·–·–)*

Table 1 *Comparison of survival times in the four treatment groups and in the control group following the induction of pancreatitis*

	n	Median survival time (h)	Interquartile range (h)	P value compared with control group
Control	10	9·5	8·8–13·4	–
Saline	10	20·3	7·9–51·4	0·236
Plasma protein solution	10	17·5	14·7–22·5	0·116
Fresh frozen plasma	10	24·8	18·8–72·0	0·01*
Aprotinin	10	19·8	14·0–23·3	0·065

* Significant, log rank test

overnight incubation at 37°C. The areas of fibrinolysis were compared with a standard curve constructed with varying concentrations of bovine trypsin (ethanol precipitate, Sigma Chemical Co, St Louis, Missouri, USA).

The trypsin inhibitory capacity of each of the four test solutions was also determined. Increasing increments of bovine trypsin were added to a 100 μl sample of each test solution, 20 μl aliquots of which were then applied to a plasminogen-free fibrin plate. The point at which fibrinolysis first appeared following overnight incubation at 37°C indicating overwhelming of the trypsin inhibitory capacity of the solution.

Statistics

Statistical analysis of the survival times was conducted by the log rank test. Simultaneous comparisons between all five groups were made with the Kruskal–Wallis test.

Results

The rats receiving intraperitoneal therapy, when studied together, had significant prolongation of their median survival compared with controls ($\chi^2 = 7\cdot19$ (1 d.f.); $P = 0\cdot007$) (*Figure 1*). When the intraperitoneal therapy groups were compared individually with the controls, only those treated with fresh frozen plasma had a significantly longer median survival (*Table 1*). Therapy with fresh frozen plasma appeared to improve survival when compared with plasma protein solution (*Figure 2*). Therapy with aprotinin appeared no better than saline alone (*Figure 3*).

Fat necrosis was found to be generalized in all animals at post mortem and histological examination of the pancreas in each confirmed acute pancreatitis. *Table 2* compares the exudate characteristics, fluid balance and morphological parameters in the groups. Macroscopic necrosis of the pancreas was invariably found in animals dying early; this always involved the head of the gland, and the remainder of the gland to a varying degree, some showing necrosis confined to the central portion of the gland around the main duct, other glands showing complete necrosis. No trend was apparent between the macroscopic appearances and the therapy administered.

Rats surviving until they were killed at 72 h all showed a similar severe pancreatic inflammation and thickening involving the entire gland. In earlier pilot studies similar changes were found to persist 1 week after the induction of pancreatitis. The type of therapy administered influenced the number of survivors at 72 h but no macroscopic or microscopic differences could be discerned between the groups.

Biochemical analyses

Neither 0·9 per cent saline solution nor plasma protein solution possessed any trypsin inhibitory capacity. Fibrinolysis first appeared after the addition of 100 μg trypsin to 100 μl fresh frozen plasma and after the addition of 450 μg trypsin to 100 μl aprotinin solution, which thus had the highest trypsin inhibitory capacity.

Exudates aspirated at 1 h demonstrated free proteolytic activity in four or five of the rats in each of the intraperitoneal therapy groups (median lysis area 215 mm^2, equivalent to 40 μg free bovine trypsin/ml) (*Table 3*). The median survival time amongst these rats (20·5 h) was not significantly different from those with no free proteolytic activity demonstrated (median survival time 21·5 h).

At post mortem examination the exudates from six of the ten control rats demonstrated free proteolytic activity (median lysis area 140 mm^2, equivalent to 27 μg free bovine trypsin/ml)

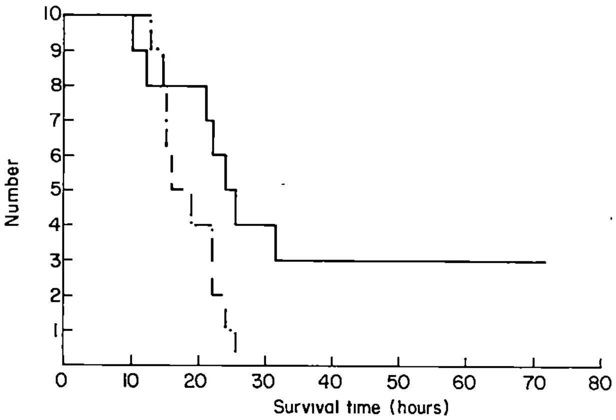

Figure 2 *Life table showing survival times in rats treated with intraperitoneal fresh frozen plasma (——) compared with human plasma protein solution (–·–·–)*

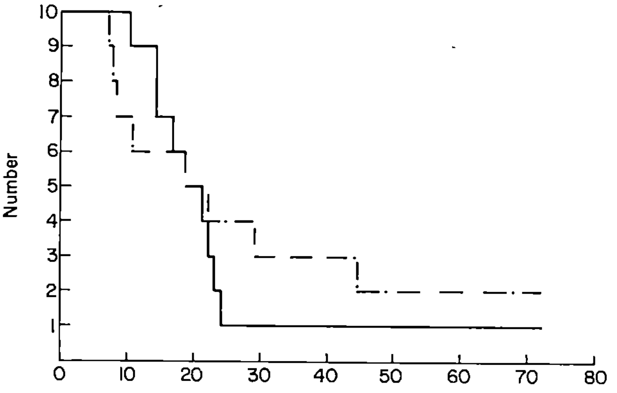

Figure 3 *Life table showing survival times in rats treated with intraperitoneal aprotinin (Trasylol®) (——) compared with saline (–·–·–)*

Table 2 *Comparability of peritoneal exudate characteristics, fluid balance and morphological parameters in the control group and in the four intraperitoneal therapy groups*

Parameter	Control group	Interperitoneal therapy groups Saline	Plasma protein solution	Fresh frozen plasma	Aprotinin	*P* value*
Body-weight (g)	186 (180–192)	187·5 (181–194)	183 (180–190)	182·5 (180–196)	184 (180–190)	n.s
Exudate volume at 1 h (ml)	–	1·3 (1–1·6)	1·6 (1·4–2·1)	1·55 (1·4–1·8)	1·3 (1·1–2·1)	n.s
Exudate colour at 1 h	–	6·5	6·5	6·5	6·5	n.s.
Net fluid balance post-therapy (ml)	2·8 (2·7–2·9)	1·75 (1·5–2·2)	1·25 (0·9–1·5)	1·5 (0·8–1·9)	1·85 (1·1–2·3)	$P<0·01$
Exudate volume at post mortem (ml)	7·5 (3·5–9·6)	5·5 (2·9–6·9)	7 (5·1–8)	3 (0·6–6)	5·5 (4·6–9·3)	n.s.
Exudate colour at post mortem	7 (6·1–7·5)	6·25 (5–7)	6·5 (5·8–6·6)	6 (5·5–7·3)	6·25 (5–7·1)	n.s
Macroscopic score						
Head	4 (4)	4 (3·8–4)	4 (4)	4 (3–4)	4 (4)	n.s.
Tail	3·5 (3–3·5)	3·25 (3–3·5)	3·5 (3–3·6)	3·25 (2·8–4)	3·5 (3–3·6)	n.s
Pancreatic weight (mg)	107 (95–121)	106 (98–126)	107 (96–115)	123 (115–137)	120 (116–143)	n.s.

Results expressed as medians (interquartile range). * Kruskal Wallis test

Table 3 *Incidence and extent of free proteolytic activity in peritoneal exudates in the five groups of rats at 1 h post-induction of pancreatitis and at post-mortem examination*

Exudate tested	Control group	Intraperitoneal therapy groups Saline	Plasma protein solution	Fresh frozen plasma	Aprotinin
1 h (*n*)	–	5/10	5/10	4/10	4/10
Median lysis area (mm^2)	–	113 (79–177)	491 (13–707)	175 (51–300)	767 (343–976)
Post mortem (*n*)	6/10	2/10	1/10	1/10	1/10
Median lysis area (mm^2)	140 (79–314)	44 (38, 50)	trace	trace	trace

Results expressed as median (interquartile ranges). *n* = number in each group of ten showing activity; median lysis area = area of zone of fibrinolysis (indicating free proteolytic activity)

(*Table 3*). Two of the rats in the saline-treated group showed residual proteolytic activity at post mortem examination (equivalent to 10 μg free bovine trypsin/ml). Only one rat in each of the other treatment groups showed a trace of activity.

Discussion

Activated proteolytic enzymes released into the circulation are quickly complexed and cleared[12], but when released into the peritoneal exudate in canine pancreatitis they may saturate the antiprotease defences, leading to hypotension and death[6]. For greatest therapeutic effect antiprotease therapy should be directed locally into the peritoneal cavity, rather than systemically where no clear benefit has been shown in several controlled clinical trials in man[13–15].

Aprotinin has previously been shown to be of no benefit when administered intraperitoneally to rats with taurocholate-induced pancreatitis[16] or mice with diet-induced pancreatitis[17] In another series of experiments in rats aprotinin added to the dialysate was found to confer no additional benefit compared with continuous, cycled peritoneal dialysis with a standard dialysate[8] but in a similar study in man, although no significant differences were shown with respect to mortality or number of complications, there was a trend in favour of this treatment[18]. The current study investigates a much simpler approach than cycled peritoneal dialysis whereby the exudate is removed by a single peritoneal lavage before instillation of the antiprotease solution.

The median survival time was significantly prolonged and the incidence and extent of free proteolytic activity in the exudate was diminished at post mortem examination in those rats which had undergone intraperitoneal therapy when compared with controls. The median survival time was the same whether the exudate removed at 1 h possessed free proteolytic activity or not. In control rats not receiving intraperitoneal therapy the median survival time did not vary whether free proteolytic activity was present at post mortem examination or not, although free proteolytic activity was not found in the animal surviving longest at 72 h. This suggests that factors other than the presence of free proteolytic activity influence the timing of death from taurocholate-induced pancreatitis.

Fresh frozen plasma and particularly aprotinin were both confirmed to possess significant trypsin inhibitory activity, whereas plasma protein solution and saline had no measurable activity. Fresh frozen plasma was the most effective of the intraperitoneal therapies tested when compared with the control group, the improvement associated with aprotinin just failing to reach statistical significance. These data suggest that the instillation of a solution possessing antiprotease activity may be superior to one possessing no activity.

Although the instillation of fresh frozen plasma was not significantly better than aprotinin, the trend towards a longer median survival in association with fresh frozen plasma suggests that the nature of the antiprotease administered, rather than its overall capacity to bind trypsin, might be the more important factor. The beneficial effect of fresh frozen plasma is likely to be due to the antiprotease α_2-macroglobulin, which preferentially binds proteases including trypsin. The α_1-antiprotease molecule, which is smaller and more abundant, accounts for the bulk (over 90 per cent) of the trypsin inhibitory capacity in plasma, but is a less effective inhibitor of trypsin The mode of clearance of aprotinin–protease and α_1-antiprotease–protease complexes from the peritoneal cavity is unknown but may, as in the circulation, involve transfer of the protease molecules to α_2-macroglobulin, and hence to the peritoneal macrophages where the complex is taken up and broken down. Thus it may be that the concentration of α_2-macroglobulin, as appears to be the case in the bloodstream, is the major rate-limiting step in the clearance of proteases from the peritoneal cavity. Provision of exogenous intraperitoneal α_2-macroglobulin in fresh frozen plasma may boost this clearance of activated proteases. Further studies examining the separate components of fresh frozen plasma may cast further light on its exact mechanism of action.

The study has demonstrated that the intraperitoneal treatment described here is simple to perform, therapeutic and that the instillation of exogenous antiproteases to the peritoneal cavity may confer additional benefit. An investigation of such an approach to the treatment of acute pancreatitis in man appears justified

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Free radical inhibition and serial chemiluminescence in evolving experimental pancreatitis

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Oxygen free radical activity and inhibition were examined in experimental pancreatitis. Twenty-five rats were randomized to five groups: controls received intravenous saline, to simulate pancreatitis one group received intravenous caerulein ($5\ \mu g\ kg^{-1}\ h^{-1}$), and three groups received sodium taurocholate via the pancreatic duct (0·2 ml, 5 per cent), either alone, following allopurinol or immediately before superoxide dismutase. Chemiluminescence (a phenomenon based on the emission of light during chemical reactions and which is dependent on oxygen free radical activity) was used as an index of oxygen free radical activity and was measured in tissue samples at 5-min intervals following induction of pancreatitis. The control mean(s.e.m.) serum amylase level 1 h after induction of pancreatitis was 635(13) units. It was significantly elevated in caerulein-induced pancreatitis, 1833(118) units (P<0·05) *and exceeded 3000 units in all taurocholate-infused animals. Mean(s.e.m.) chemiluminescence ranged from 44 (8) mV 100 mg^{-1} at time zero to 404(113) mV 100 mg^{-1} at 1 h in controls. In caerulein-induced pancreatitis mean(s.e.m.) chemiluminescence peaked at 20 min (1399(239) mV 100 mg^{-1},* P<0·02) *and in taurocholate-induced pancreatitis at 15 min (2316(95) mV 100 mg^{-1},* P<0·004). *Superoxide dismutase significantly reduced chemiluminescence and hyperamylasaemia in taurocholate groups. Increasing oxygen free radical activity paralleled evolving pancreatitis. Superoxide dismutase may have a therapeutic role in pancreatitis.*

Keywords: Pancreatitis, oxygen-derived free radicals, chemiluminescence

The prognosis in acute pancreatitis appears to be related to clinical and biochemical status in the early phase of the disease[1,2] Although surgery may benefit those with pancreatic necrosis[3] or gallstone pancreatitis[4], in the majority of cases surgical intervention does not seem to improve outcome[5]. This inability to alter the course of the disease has spurred interest in the aetiology of the cellular and microvascular changes at the onset of acute pancreatitis

Studies designed to elucidate the pathophysiology of acute pancreatitis would suggest that, irrespective of the precipitating agent or event, a common pathway may be involved through which the local and systemic effects of this disease are mediated. In a variety of experimental models, e.g. gallstones[6], ischaemia[7] and alcohol[8], endothelial injury and increased capillary permeability have been demonstrated Increased oxygen-derived free radical activity has been proposed as the mechanism by which alterations in the microvasculature are mediated[9] These unstable and highly reactive toxic metabolites of molecular oxygen, O_2^-, OH^- and H_2O_2, have wide-ranging effects on cells and tissues, including peroxidation of lipids, denaturing of enzymes and proteins, and acceleration of tryptic activity[10,11].

The assumption that these agents are responsible for the changes of pancreatitis is largely based on indirect evidence. Known inhibitors of free radical generation and activity have been observed to limit the *ex vivo* changes associated with pancreatitis[9], i.e. weight gain and hyperamylasaemia in the isolated perfused pancreas.

In the following experiments, pancreatic tissue chemiluminescence was used to assess free radical activity in evolving pancreatitis following *in vivo* retrograde infusion of taurocholate in the pancreatic duct or intravenous caerulein infusion. Pancreatic tissue chemiluminescence, the emission of light secondary to electron transfer in chemical reactions, was used as a direct index of free radical activity because the phenomenon gives real-time information on the extent of oxygen activation at any given moment[12]. This is particularly relevant to the study of oxygen free radical activity in organic samples because the majority of reactions in biological systems require oxygen to become luminescent (its unique electron structure favours excited intermediates and its reduction is associated with a high energy which is easily measured as intensity of light emission)[12,13]. In addition, clinical indices of pancreatitis, serum amylase and an altered histological pattern, were studied together with the effects of superoxide dismutase (a free radical scavenger) and allopurinol (a xanthine oxidase inhibitor) on both chemiluminescence and amylasaemia.

The aim was to provide direct evidence for the role of free radicals in pancreatitis and to investigate the potential of free radical detoxification in this disease.

Materials and methods

Models of pancreatitis

Male Sprague-Dawley rats (340–380 g, $n=25$) were used in all experiments following induction of anaesthesia with intraperitoneal chloral hydrate (100 mg kg^{-1}) In the control group ($n=5$), the jugular vein was cannulated and perfused with 0 2 ml 0 9 per cent sodium chloride Oedematous pancreatitis was induced ($n=5$) by intrajugular infusion of caerulein ($5\ \mu g\ kg^{-1}\ h^{-1}$ in the same volume as in controls) Severe haemorrhagic pancreatitis was induced ($n=5$) by retrograde infusion of 0 2 ml 5 per cent sodium taurocholate via the pancreatic duct After 1 h all animals were killed by intravenous injection of supersaturated potassium hydroxide.

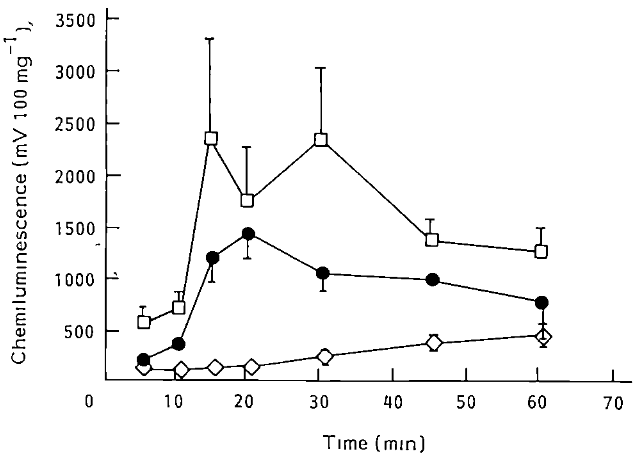

Figure 1 *Serial pancreatitic tissue mean(s e m.) chemiluminescence in evolving pancreatitis,* □, *taurocholate-infused group,* ●, *caerulein-infused group,* ◇, *control group*

Free radical detoxification

In models of severe pancreatitis the effects of allopurinol (xanthine oxidase inhibitor) and superoxide dismutase (a free radical scavenger) were investigated For each substance, severe pancreatitis was induced in five animals by taurocholate infusion as above Allopurinol (15 mg kg^{-1}) was administered orally for 2 days, then intraperitoneally before and at the induction of pancreatitis. Superoxide dismutase (15 000 units per rat) was infused via the pancreatic duct immediately after taurocholate infusion.

Assessment of free radical activity in pancreatic tissue

Animals were anaesthetized in groups as above and at intervals of 5, 10, 15, 20, 30, 45 and 60 min after induction of pancreatitis biopsies of pancreatic tissue (approximately 1 mm^3) were taken with a scalpel at laparotomy and subsequently weighed These samples were immediately placed in a solution containing 400 μl of buffer (phosphate buffered saline, 1 mM HEPES buffer and 5 mM glucose), 40 μl Luminol® (2 mg ml^{-1} in phosphate buffered saline) and 20 μl 30 per cent triethylamine (all reagents were supplied by Sigma Chemical Company, Poole, UK).

Chemiluminescence was assessed in a Wallac LKB (Gaithersberg, Maryland, USA) luminometer and mean chemiluminescence (mV per 100 mg tissue sample) for each group of five animals was noted for each time interval.

Chemiluminescence reflects oxidative metabolism in cells, particularly in those reactions in which oxygen free radicals are involved[12] The resulting light emission can be amplified by 10^4 by use of 5-amino-2,3-dihydro-1,4-phthalazinedione (Luminol), a substance with a high chemiluminescent quantum which emits an intense light upon oxidation proportional to the superoxide ion activity[12] Therefore, the technique reflects instantaneous free radical activity. Because of the limitations imposed by the small volume of rat pancreas available and the need for study of biopsies from the same pancreas over seven successive time periods, only one sample from each animal could be taken for assessment of chemiluminescence Reproducibility by variation in batch assay could not be assessed since chemiluminescence requires immediate estimation once a sample is taken, and the luminometer deals with only one sample at a time. Reproducibility of readings, however, was evidenced by the fact that all the recorded values for the first 20 min (20 observations) in saline-infused controls were <120 mV 100 mg^{-1}, mean(s e m) 54·3(6·9), whereas 19 of 20 observations following caerulein were >120 mV 100 mg^{-1}, mean(s e.m.) 750(146), as were 19 of 20 observations following taurocholate infusion, mean(s e m) 1289(311) mV 100 mg^{-1}

Serum amylase

One hour after induction of pancreatitis, 0·5 ml portal venous blood was aspirated and serum amylase was estimated by standard assay The upper limit of serum amylase resolution was 3000 units

Histology

At 60 min remaining pancreatic tissue was excised, fixed in formal-saline and later examined following haematoxylin and eosin staining

Statistics

All values are expressed as mean(s.e.m) Chemiluminescence values for each group were compared using a paired t test of the means for each time point in the study, while a non-paired t test was used for comparison of mean amylase values

Results

Pancreatic tissue chemiluminescence in evolving pancreatitis

Mean chemiluminescence was estimated for each of three groups (controls, taurocholate infusion and caerulein infusion) In controls, mean(s e m.) chemiluminescence at 5 min was 44(8) mV 100 mg^{-1} and reached a peak of 404(113) mV 100 mg^{-1} at 60 min (*Figure 1*).

In contrast, mean(s.e.m) chemiluminescence values after caerulein infusion were significantly higher ($P<0\cdot02$) and ranged from 189(54) to 1399(239) mV 100 mg^{-1} (*Figure 1*). Similarly, values following taurocholate infusion were also higher than controls ($P<0\cdot004$) and ranged from 503(182) to 2613(953) mV 100 mg^{-1} (*Figure 1*) After both caerulein and taurocholate infusions, chemiluminescence activity appeared to increase to a maximum, at 20 and 15 min respectively, and thereafter gradually declined

Serum amylase following induction of pancreatitis

Mean(s e m.) serum amylase at 60 min in controls was 635(13) units (*Figure 2*) Following caerulein and taurocholate infusions amylase was significantly higher than in controls For caerulein it was 1833(118) units ($P<0\cdot05$) and for taurocholate it was >3000 units in all animals ($P<0\cdot05$) (*Figure 2*)

Histology

No differences in histology were observed between the control group and the mild pancreatitis group. Minimal oedema was seen in a number of animals following taurocholate infusion and in some which had received adjuvant allopurinol or superoxide dismutase

Effect of superoxide dismutase in taurocholate-induced pancreatitis

Treatment with superoxide dismutase following taurocholate infusion caused a significant reduction in chemiluminescence, mean(s.e m.) range from 189(54) to 1399(239) mV 100 mg^{-1},

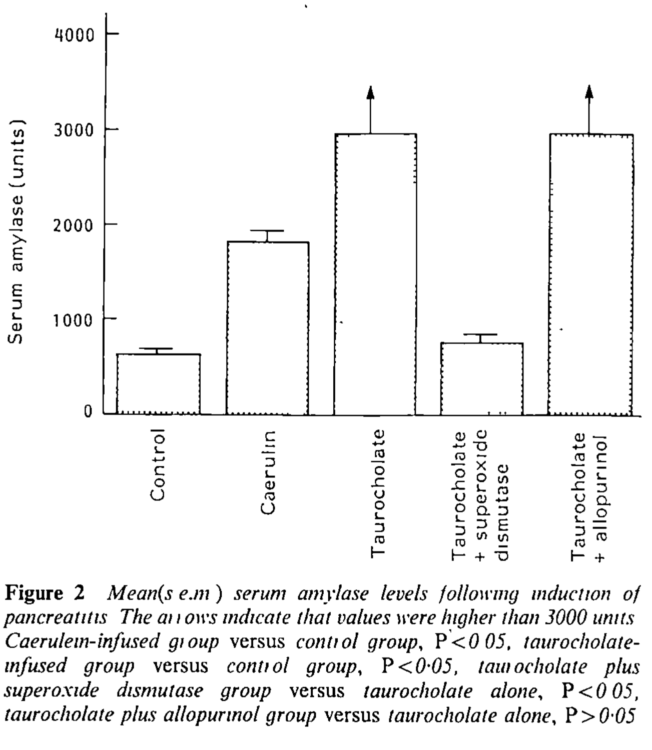

Figure 2 *Mean(s e.m) serum amylase levels following induction of pancreatitis The arrows indicate that values were higher than 3000 units Caerulein-infused group* versus *control group,* $P<0\cdot05$, *taurocholate-infused group* versus *control group,* $P<0\cdot05$, *taurocholate plus superoxide dismutase group* versus *taurocholate alone,* $P<0\cdot05$, *taurocholate plus allopurinol group* versus *taurocholate alone,* $P>0\cdot05$

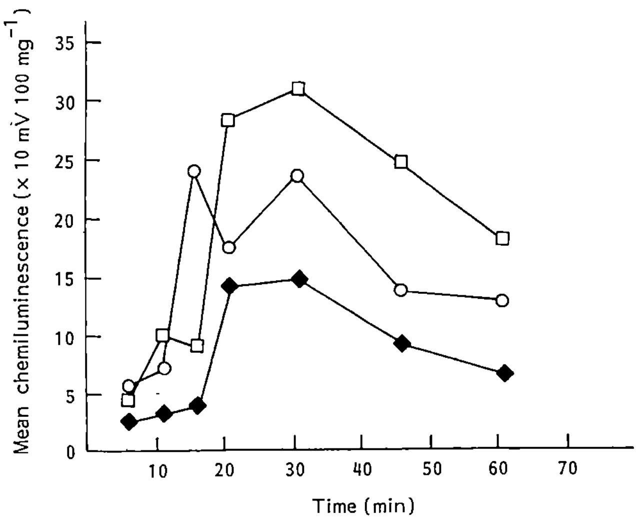

Figure 3 *Effect of superoxide dismutase and allopurinol on mean chemiluminescence in taurocholate-induced pancreatitis* ○, *taurocholate-infused group,* ◆, *taurocholate plus superoxide dismutase group,* □, *taurocholate plus allopurinol group; taurocholate plus superoxide dismutase* versus *taurocholate alone,* $P<0\cdot02$, *taurocholate plus allopurinol* versus *taurocholate alone,* $P>0\cdot05$

compared with from 503(182) to 2316(953) mV 100 mg^{-1} without superoxide dismutase ($P<0\cdot02$) (*Figure 3*). Similarly, treatment with superoxide dismutase resulted in significantly lower levels of amylase, i.e. 789(60) units following taurocholate and superoxide dismutase infusion compared with >3000 units for each animal for taurocholate alone ($P<0\cdot05$) (*Figure 2*).

Effect of allopurinol pretreatment in taurocholate-induced pancreatitis

In contrast with superoxide dismutase treatment, pretreatment with allopurinol did not result in a decrease in chemiluminescence (mean(s.e.m.) range from 363(213) to 3017(669) mV 100 mg^{-1}; $P>0\cdot05$) (*Figure 3*) or serum amylase >3000 units in each animal ($p>0\cdot05$) (*Figure 2*).

Discussion

Intravenous caerulein infusion has previously been used as a model of experimental pancreatitis to illustrate the microvascular changes in both the liver and pancreas which frequently accompany this disease[14,15] This technique is known to result in an oedematous form of pancreatitis[16]. Retrograde infusion of taurocholate is also an accepted model of pancreatitis and is based on the premise that both pancreatic duct obstruction[17] and bile reflux[18] are important aetiological factors in pancreatitis. This particular model is known to result in severe haemorrhagic pancreatitis[19]. A number of other techniques have also been investigated, e.g. ischaemia[7], pancreatic duct obstruction[6] and alcohol perfusion[8]. All result in pancreatitis[6–8]. The wide variety of experimental models available for simulation of pancreatitis coupled with the recognition of numerous important aetiological factors in human pancreatitis suggest a multifactorial aetiological basis for the disease. However, the similarity in the manifestations of the resulting disease process at the cellular and microvascular level implies a final common pathway in the mediation of the associated tissue destruction. Increased capillary permeability mediated by oxygen-derived free radicals is one suggested pathway[9].

Oxygen free radicals are produced predominantly by activated neutrophils and are thought to have important antibacterial effects[20]. In addition to neutrophils, cells in other tissues may produce these radicals under appropriate stimulation[21]. In the presence of ischaemia or a triggering event, excessive production of these agents may occur and this process is accelerated in the face of reoxygenation or reperfusion[10,11]. Once initiated, the process is self-perpetuating[10,11]. The ensuing chain reaction and excess of free radicals have the potential to cause microvascular disruption in many tissues leading to increased capillary permeability and fluid transudation. This mechanism of injury has also been incriminated in the tissue damage associated with many other conditions, e.g. cardiac reperfusion injury[22], adult respiratory distress syndrome[23], cold ischaemia damage to kidney grafts[24] and gastric stress ulceration[25].

The use of free radical inhibitors has been reported to inhibit many of the changes associated with pancreatitis[6–9]. This has led to speculation that excessive free radical activity may be responsible for initiating pancreatitis[9]. A direct link between oxygen free radicals and pancreatitis is difficult to demonstrate because the half-life of these oxygen-derived radicals is in microseconds, rendering quantitative assessment difficult[26]. Tissue chemiluminescence is a technique that allows estimation of radical activity by assessing the physical effects of free radicals, i.e. the characteristic light emission from cells undergoing peroxidation by free radicals[12].

In these experiments, evidence for increased free radical activity was found in two different models of pancreatitis. At an early stage following induction of pancreatitis, chemiluminescence values were elevated compared with controls. This elevation appeared to be higher in the taurocholate model which is known to be associated with a more aggressive type of pancreatitis[19] than the oedematous form often observed after caerulein infusion[16]. Moreover, haemorrhagic pancreatitis in humans is associated with a high mortality rate[5], and in these experiments it was also shown to be associated with higher levels of serum amylase. These results suggest that free radical activity parallels the onset of pancreatitis and is higher in the model of pancreatitis reported to be associated with an aggressive haemorrhagic type of disease process, i.e. the taurocholate infusion model.

In both models chemiluminescence appeared to peak at between 15 and 30 min and thereafter decreased toward the level observed in controls. It has previously been suggested that microvascular disruption is an integral component of the progression of tissue damage in pancreatitis[14,15,27]. Moreover electronmicroscopic changes have been demonstrated in acinar cells soon after induction of pancreatitis, i.e. before microvascular change[15]. Therefore, the short-lived burst of free radical activity seen in the present experiments may be the precipitating event which causes microvascular injury. This injury in turn may sustain increased vascular permeability and the resulting oedema and haemorrhage frequently observed in pancreatitis. This hypothesis may explain why significant benefit may be derived from agents such as allopurinol only if they are used prophylactically in tissues known to have the potential for excessive xanthine oxidase activity (to prevent the free radical burst) and why their later use appears to have little effect[7–9].

Using superoxide dismutase the levels of chemiluminescence normally expected after infusion of taurocholate were significantly reduced. Superoxide dismutase scavenges radicals already produced[10,11]. Its action is not dependent on anticipation of the free radical burst, but rather on scavenging the products, i.e. free radicals. The resulting diminution of chemiluminescence following the use of superoxide dismutase was accompanied by a corresponding decrease in amylase to levels not significantly different from those in controls. This raises the possibility that pancreatitis did not occur in animals receiving taurocholate and superoxide dismutase. These data further support the concept of a prime role for oxygen-derived free radicals in evolving pancreatitis

In contrast to the beneficial results obtained with superoxide dismutase, prophylaxis with allopurinol did not reduce chemiluminescence or serum amylse levels. This may simply reflect inadequate dosage or poor timing of administration, because other authors have found allopurinol to be beneficial in the prevention of the pathological changes associated with pancreatitis[9]. However, allopurinol is a specific xanthine oxidase inhibitor and it has been suggested that xanthine oxidase levels are low in pancreatic tissue[28]; benefit from prophylaxis with allopurinol is not a univesal finding[29]. Furthermore, many of the experiments in which allopurinol has been shown to be of benefit were performed in *ex vivo* perfused pancreas preparations[7–9], unlike the *in vivo* models used in these present experiments. In addition, xanthine oxidase levels appear to vary extensively depending on the method of assay and also on the species in which the estimates are made[28]. There is dispute as to whether pancreatic tissue is in fact the main source of radical production in pancreatitis[29]. Recruited neutrophils could also be a significant source[10,11]. In any event, an approach based on the scavenging of radicals, rather than an attempt at blocking specific pathways of free radical production, may be more appropriate because such an approach is applicable regardless of the chief site of radical production.

In pancreatitis tissue destruction is not confined to the pancreas and it has been reported that similar vascular disruption also occurs in the gut, liver, lung and kidney. Involvement of these distant organs adds significantly to the related morbidity and mortality[5]. If free radicals are involved in the mediation of distant organ effects, as would appear likely because the pathological microvasculature is similar[14,15], then free radical scavenging may also limit these effects. Furthermore, the similarity of the effects on different organs lends support to the possibility that freely diffusable agents, capable of immense vascular damage and emanating from components of circulating blood, might be a major factor in the mediation of this disease. Toxic radicals fulfil these criteria[10,11].

These *in vivo* experiments provide further direct evidence for the role of oxygen-derived free radicals in evolving pancreatitis. The inability of allopurinol to inhibit both chemiluminescence and hyperamylasaemia suggests a source other than xanthine oxidase for free radical production in pancreatitis, although the dosage and timing of administration of this agent merits further study.

Free radical scavenging with superoxide dismutase administered via the pancreatic duct was observed to inhibit chemiluminescence and hyperamylasaemia. Further studies with this agent may elucidate whether these same benefits are observed following its systemic administration. The early peak and short-lived duration of elevated oxygen free radical activity may, however, preclude the efficient use of superoxide dismutase in human patients in whom the diagnosis of pancreatitis or the admission to hospital has been delayed.

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Prediction of outcome in acute pancreatitis: a comparative study of APACHE II, clinical assessment and multiple factor scoring systems

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The APACHE II severity of disease classification system has been examined prospectively in 160 patients with acute pancreatitis. Using clinical and simple laboratory data APACHE II was able to provide useful discrimination between uncomplicated, complicated and fatal attacks within a few hours of admission. Peak APACHE II scores (recorded during the first 3 days) had a prognostic accuracy similar to the multiple factor scoring systems, but then incurred a similar delay. Patients could be graded according to their risk of death or of developing a major complication; no deaths occurred in patients with a peak APACHE II score <10. APACHE II can be repeated daily, uncomplicated attacks demonstrating falling scores in association with clinical improvement, in contrast to the rising scores associated with clinical deterioration in those dying early. APACHE II appears to reflect any continuing disease activity and may prove a useful means of monitoring the course of the illness and response to therapy.

Keywords: Acute pancreatitis, prediction of outcome, APACHE II

Drawbacks of the standard multifactorial scoring systems for grading severity in acute pancreatitis[1,2] include their inherent delay in characterizing disease severity. Furthermore, as they provide for 'once only' prediction within the first 48 h of admission, they cannot be measured sequentially to permit objective monitoring during the course of the illness

The APACHE illness grading system (acute physiology and chronic health evaluation) was reported by Knaus and colleagues in 1981[3] based on the premise that the severity of an acute disease could be measured by quantifying the degree of abnormality of multiple physiological variables. The original APACHE system provided weightings (from 0–normal to 4–most abnormal) for 34 potential physiological and laboratory measurements, each being determined from the most abnormal recording made during that particular 24 h period. The sum of all the measurements recorded represented the acute physiology score, the higher the score the sicker the patient[3]. To this was added an assessment of the patient's pre-admission health status (A–fit to D–severely compromised health) to give the overall APACHE classification.

The original APACHE system was complex and difficult to use prompting simplifications by other groups[4] A much simplified modification, the APACHE II, was reported in 1985[5]. APACHE II utilized only 12 routinely available physiological and laboratory measurements with an additional weighting for age and pre-admission health status. An increasing APACHE II score was found to correlate with the subsequent risk of hospital death[5].

To date APACHE II has been studied most often in patients in intensive care units[5] and in predicting the outcome of intra-abdominal sepsis[6]. In an initial report from Leeds it was suggested to be of value in acute pancreatitis, predicting the outcome from an attack with greater accuracy than the standard multiple factor scoring systems[7].

The aims of the current study were to evaluate APACHE II prospectively in patients with acute pancreatitis and compare it with clinical assessment and two widely utilized illness-specific multiple factor scoring systems[1,2]

Patients and methods

We studied 160 consecutive patients with acute pancreatitis admitted to the Royal Infirmary, Glasgow and five nearby hospitals (see acknowledgements) between February 1986 and July 1987. The diagnosis was based on the presence of a serum amylase level ⩾1200 units/l with a compatible clinical picture

Clinical assessment

Each patient underwent clinical assessment on admission by one of the authors (C W) The attack was graded as mild, moderate or severe based on the presence or absence of shock, the adequacy of the peripheral perfusion and urine output, the presence of respiratory distress, fever, body wall staining and on the degree of abdominal tenderness, distension and ileus. Attacks were graded as mild when an uncomplicated recovery was considered likely and as severe when death or a major complication was considered the likely outcome Attacks falling between these two definitions were graded as moderate. This assessment was subjective and made without reference to biochemical or other laboratory results The assessment was repeated 24 h and 48 h after admission.

APACHE II determination

Appropriate laboratory and physiological data were recorded prospectively for 7 days, or until discharge if sooner, to permit calculation of the APACHE II score[5] (*Table 1*), Ranson[1], and Glasgow scores[2] (*Table 2*). The modification of the Ranson scoring system for attacks associated with gallstones[8] was not employed as the diagnosis of gallstones was rarely available on admission. Laboratory data (sodium, potassium, creatinine, haematocrit, white cell count and arterial pH and P_{O_2}) were recorded at least daily. Physiological data (temperature, heart rate, mean blood pressure and respiratory rate) were recorded at least 6-hourly and the Glasgow Coma Scale scored daily For each factor the most abnormal recording during that 24-h period was used for calculation of the APACHE II score Weightings for age and chronic health state were added to give the final score.

Aetiology and outcome

Gallstones were identified in 59 patients (37 per cent), 50 (31 per cent) had a history of alcohol abuse and in six patients (4 per cent) both factors were present Other recognized aetiological factors were implicated in 13 patients (8 per cent) and in 32 (20 per cent) no associated aetiological factors could be identified Three patients were subsequently excluded. two because of alternative diagnoses made following diagnostic peritoneal lavage (mesenteric venous infarction and haemoperitoneum due to traumatic transection of the pancreas) and the third because of suspected aortic aneurysm rupture

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Table 1 *The APACHE II severity of disease classification system*

	High abnormal range					Low abnormal range			
Physiological variable	+4	+3	+2	+1	0	+1	+2	+3	+4
Temperature, rectal (°C)	≥41	39–40·9		38·5–38·9	36–38·4	34–35·9	32–33·9	30–31·9	≤29·9
Mean arterial pressure (mmHg)	≥160	130–159	110–129		70–109		50–69		≤49
Heart rate (ventricular response)	≥180	140–179	110–139		70–109		55–69	40–54	≤39
Respiratory rate (non-ventilated or ventilated)	≥50	35–49		25–34	12–24	10–11	6–9		≤5
Oxygenation A_{aDO_2} or P_{aO_2} (mmHg)									
F_{IO_2} ≥0·5 record A_{aDO_2}	≥500	350–499	200–349		<200				
F_{IO_2} <0·5 record only P_{aO_2}					P_{O_2} >70	P_{O_2} 61–70		P_{O_2} 55–60	P_{O_2} <55
Arterial pH	≥7·7	7·6–7·69		7·5–7·59	7·33–7·49		7·25–7·32	7·15–7·24	<7·15
Serum sodium (mmol/l)	≥180	160–179	155–159	150–154	130–149		120–129	111–119	≤110
Serum potassium (mmol/l)	≥7	6–6·9		5·5–5·9	3·5–5·4	3–3·4	2·5–2·9		<2·5
Serum creatinine (mg/100 ml) (Double point score for acute renal failure)	≥3·5	2–3·4	1·5–1·9		0·6–1·4		<0·6		
Haematocrit (%)	≥60		50–59·9	46–49·9	30–45·9		20–29·9		<20
White blood count (×10³/mm³)	≥40		20–39·9	15–19·9	3–14·9		1–2·9		<1
Glasgow coma score (GCS): Score = 15 − actual GCS									
Total acute physiology score (APS). Sum of the 12 individual variable points									
Serum HCO_3 (venous-mmol/l) (Not preferred, use if no ABGs)	≥52	41–51·9		32–40·9	22–31·9		18–21·9	15–17·9	<15

APACHE II score is given by the sum of the acute physiology score, the age points, and the chronic health points. Age points are assigned: age ≤44, zero; 45–54, 2 points, 55–64, 3 points, 65–74, 5 points; and ≥75, 6 points. Chronic health points are assigned if the patient has a history of severe organ system insufficiency or is immunocompromised as follows: for non-operative or emergency postoperative patients, 5 points, and for elective postoperative patients, 2 points. Organ insufficiency or an immunocompromised state must have been evident before hospital admission and must conform to the following criteria: *liver*, biopsy proven cirrhosis and documented portal hypertension, episodes of past upper gastrointestinal bleeding attributed to portal hypertension, or prior episodes of hepatic failure/encephalopathy/coma; *cardiovascular*, New York Heart Association Class IV (i.e. symptoms of angina or cardiac insufficiency at rest or during minimal exertion), *respiratory*, chronic restrictive, obstructive, or vascular disease resulting in severe exercise restriction, i.e. unable to climb stairs or perform household duties, or documented chronic hypoxia, hypercapnia, secondary polycythemia, severe pulmonary hypertension (>40 mmHg), or respirator dependency, *renal*, receiving chronic dialysis, and, *immunocompromised*, the patient has received therapy that suppresses resistance to infection, e.g. immunosuppression, chemotherapy, radiation, long-term or recent high dose steroids, or has a disease that is sufficiently advanced to suppress resistance to infection, e.g. leukaemia, lymphoma, AIDS. A_{aDO_2}, alveolar-arterial oxygen difference, P_{aO_2}, arterial partial pressure of oxygen; F_{IO_2}, fraction of inspired oxygen, ABGs, arterial blood gases

Table 2 *Objective prognostic factors comprising the Ranson*[1] *and Glasgow*[2] *multiple factor scoring systems*

Ranson*	Glasgow
On admission	Within 48 h
Age >55 years	Albumin <32 g/l
WCC >16 000/mm³	WCC >15 000/mm³
LDH >600 units/l	LDH >600 units/l
AST >120 units/l	AST/ALT >200 units/l
Glucose >10 mmol/l	Glucose >10 mmol/l
	Calcium <2 mmol/l
Within 48 h	Urea >16 mmol/l
	P_{O_2} <60 mmHg
Haematocrit fall >10%	
Urea rise >0·9 mmol/l	
Calcium <2 mmol/l	
P_{O_2} <60 mmHg	
Base deficit >4 mEq/l	
Fluid sequestration >6000 ml	

Either scoring system ≥3 factors positive = severe disease. * Ranson factors modified to equivalent SI or local units. WCC, white cell count; LDH, lactate dehydrogenase, AST, aspartate transaminase, ALT, alanine transaminase

Thus 157 patients were analysed, 12 (7·6 per cent) of whom had a fatal outcome recorded. A complicated outcome was recorded in 26 further patients (16·6 per cent) who survived and the remainder had an uncomplicated clinical course. A complicated outcome was defined as the development of a local pancreatic complication – necrosis (necrotic pancreatic and/or peripancreatic tissue recovered at laparotomy), abscess or pseudocyst, or a systemic complication – acute respiratory insufficiency (P_{O_2}<60 mmHg, requiring ventilation or oxygen therapy by mask for greater than 5 days), renal failure (urine volume <400 ml/24 h with a rising blood urea and no response to 24 h fluid therapy), left ventricular failure (pulmonary oedema diagnosed clinically supported by characteristic changes on chest radiography) or septicaemia.

Statistics

Results are expressed as mean(s.e.m.). Statistical analyses were conducted by the Mann–Whitney *U* test, χ^2 test, Fisher's exact test and Spearman rank correlation. The diagnostic performance of the scoring systems have been analysed by sensitivity, specificity, predictive value and efficiency[9].

Results

Admission APACHE II

The mean APACHE II scores of patients with a complicated or fatal outcome were each significantly different from those with an uncomplicated outcome (9·35(0·8) and 14·2(1·8) respectively *versus* 6·29(0·38), both $P<0·001$), the admission scores often being the most abnormal recorded. The 'cut-off' score providing the best discrimination was calculated by taking the highest product of the sensitivity and specificity and was found for an APACHE II score of >5 (*Table 3*). Raising the cut-off to >7 resulted in a slightly greater overall accuracy with some loss of sensitivity. *Table 3* also details the diagnostic

Table 3 *Analysis of admission and peak APACHE II scores and comparison with multiple factor scoring systems in the prediction of outcome from acute pancreatitis*

	Sensitivity (%)	Specificity (%)	Predictive value positive (%)	Predictive value negative (%)	Percentage correct
Clinical assessment					
On admission	34	98	87	83	83
At 24 h	47	100	100	86	87
At 48 h	44	100	100	86	87
On admission					
APACHE II (>5)	95	54	40	97	64
APACHE II (>7)	68	67	40	87	68
Peak					
APACHE II (>9)	82	74	50	93	76
APACHE II (>12)	53	92	69	86	83
Glasgow score	71	88	66	91	84
Ranson score	87	71	49	94	75

Peak APACHE II score = highest score in day 1–3; sensitivity = percentage of all complicated attacks predicted correctly by test; specificity = percentage of all mild attacks predicted correctly by test; predictive value positive = percentage of complicated attacks among all predicted severe by test, predictive value negative = percentage of mild attacks among all predicted mild by test, percentage correct = percentage correctly classified

Table 4 *Examination of the value of the 14 individual parameters comprising the admission APACHE II score in discriminating complicated and fatal attacks from uncomplicated attacks*

Parameter	Complicated/ uncomplicated attack	Number of patients scoring	Weighting score distribution 1	2	3	4	5	6	P value
Sodium	Complicated	2	2						n s.
	Uncomplicated	1	1						
Potassium	Complicated	9	7	1		1			$P<0{\cdot}05$
	Uncomplicated	9	8			1			
Creatinine	Complicated	9		5	1	2		1	n s.
	Uncomplicated	12		11	1				
Arterial pH	Complicated	3		2		1			n.s.
	Uncomplicated	7	4	2	1				
Arterial P_{O_2}	Complicated	17	7		3	7			$P<0{\cdot}02$
	Uncomplicated	27	17		6	4			
Haematocrit	Complicated	7	4	3					n s.
	Uncomplicated	24	18	6					
White cell count	Complicated	9	4	5					n s.
	Uncomplicated	23	15	8					
Temperature	Complicated	17	16			1			n.s.
	Uncomplicated	39	39						
Heart rate	Complicated	25		19	6				$P<0{\cdot}02$
	Uncomplicated	50		43	7				
Mean blood pressure	Complicated	26		19	5	2			n.s
	Uncomplicated	63		49	13	1			
Respiratory rate	Complicated	15	12		3				$P<0{\cdot}001$
	Uncomplicated	11	10		1				
Glasgow score	Complicated	2		1	1				n s
	Uncomplicated	3	2	1					
Age	Complicated	31		5	10		11	5	$P<0{\cdot}01$
	Uncomplicated	64		11	20		20	13	
Chronic health evaluation	Complicated	1					1		n.s
	Uncomplicated	2					2		

Statistical analysis by χ^2 and Fisher's exact test

of clinical assessment and the other illness-specific prognostic scoring systems.

When the 14 individual components of the admission APACHE II score were examined potassium, P_{O_2}, heart rate, respiratory rate and age were each found to separate the uncomplicated attacks from complicated or fatal attacks. Only a modest correlation was found between the P_{O_2} and the respiratory rate ($r=0{\cdot}294$). Sodium, the Glasgow Coma Scale and the chronic health evaluation were abnormal in very few patients (*Table 4*).

Peak APACHE II

Better discrimination between uncomplicated, complicated and fatal attacks was provided if the peak APACHE II score (recorded during the first 3 days) was used. A peak score of >9 provided a sensitivity of 82 per cent with 76 per cent of attacks being predicted correctly, rising to 83 per cent if the cut-off was raised to >12 (*Table 3*). The distribution of the scores is shown in *Figure 1*. As the peak APACHE II score recorded increased so too did the incidence of death and complication (*Figure 2*). No deaths occurred among the 95 patients with a peak APACHE II score of <10 and only six (6 per cent) developed a complication. *Table 5* details the diagnostic performance of the scoring systems for attacks associated with gallstones and alcohol respectively.

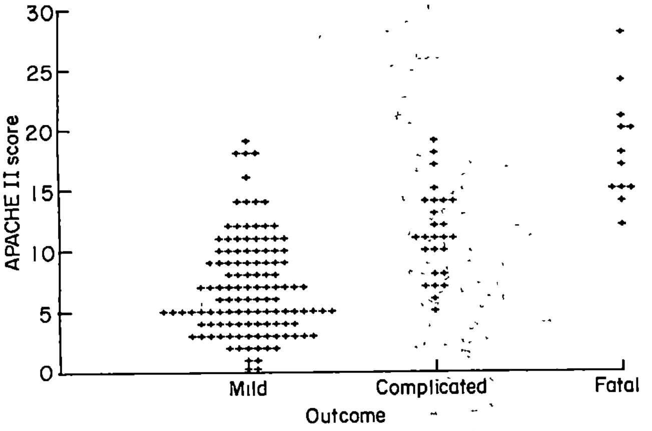

Figure 1 *Scattergram shows the distribution of the peak APACHE II scores (recorded during days 1–3) in relation to the outcome from acute pancreatitis*

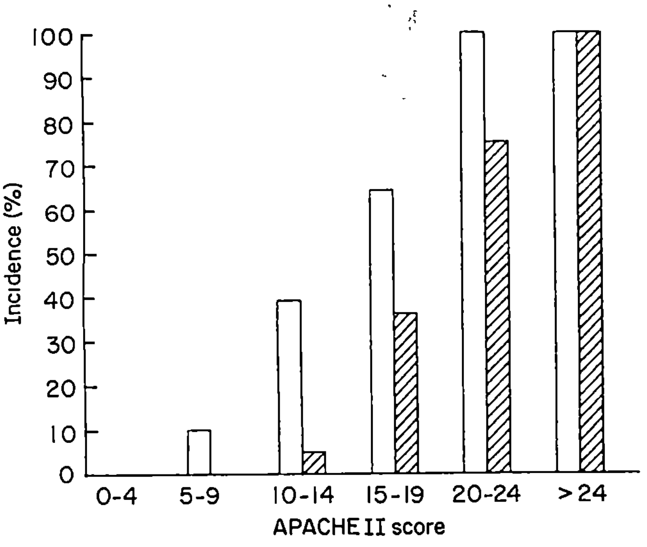

Figure 2 *Incidence of death* (▨) *and morbidity* (□) *from acute pancreatitis in relation to the peak APACHE II score recorded*

Monitoring the course of illness

Figure 3 shows the daily mean APACHE II scores plotted for each of the patient groups. Patients with an uncomplicated attack demonstrated a steady fall of their APACHE II scores each day with resolution of the attack. Patients with a complicated outcome who survived showed a higher but similar overall pattern. A different pattern was observed in those with a fatal outcome, demonstrating an early rise in their APACHE II scores, peaking on the third day before falling. This group also demonstrated persistent elevation of their physiological data scores, presumably reflecting continuing disease activity.

No overall differences were found in the mean APACHE II scores whether the attacks were complicated by local pancreatic or systemic complications. Patients manifesting early complications had higher mean APACHE II scores, persisting throughout the first week, compared with the falling scores in those who subsequently developed late complications, these differences reaching significance on the third, fifth, sixth and seventh days. If a peak APACHE II score of >9 is selected as the cut-off for predicting a complicated attack then 87·5 per cent of those developing early complications would be correctly identified compared with only 50 per cent of those developing a late complication. The design of the study did not allow for continued monitoring to determine whether a secondary increase in the APACHE II score preceded the development or detection of a late complication.

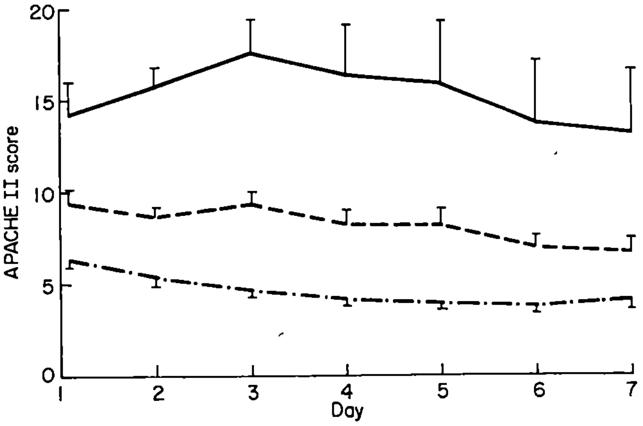

Figure 3 *Mean daily APACHE II scores by outcome in 119 patients with an uncomplicated course* (–·–·–), *26 patients with a complicated course* (– – – –) *and 12 patients with a fatal outcome* (——) *The differences between fatal and uncomplicated and between complicated and uncomplicated were highly significant* (P<0·001) *for each day* (*Mann–Whitney* U *test*)

Table 5 *Comparison of peak APACHE II score and multiple factor scoring systems for alcohol and gallstone-associated attacks of acute pancreatitis*

	Sensitivity (%)	Specificity (%)	Predictive value positive (%)	Predictive value negative (%)	Percentage correct
Gallstone					
Peak APACHE II (>9)	93	66	45	97	72
Glasgow score	64	78	47	88	75
Ranson score	86	52	35	92	60
Alcohol					
Peak APACHE II (>9)	57	88	44	92	83
Glasgow score	57	98	80	93	92
Ranson score	86	98	86	98	96

Peak APACHE II score = highest score in day 1–3; sensitivity = percentage of all complicated attacks predicted correctly by test; specificity = percentage of all mild attacks predicted correctly by test; predictive value positive = percentage of complicated attacks among all predicted severe by test; predictive value negative = percentage of mild attacks among all predicted mild by test; percentage correct = percentage correctly classified

Discussion

Prospective assessment of the APACHE II severity of disease classification system has been shown to provide objective discrimination between uncomplicated, complicated and fatal attacks of acute pancreatitis within a few hours of admission to hospital. The laboratory tests required are simple, routine and readily available 'out of hours' which is not generally the case for the calcium and enzyme assays required for the Ranson[1] and Glasgow[2] multiple factor scoring systems. Clinical assessment, although shown to have the highest overall accuracy of prediction on admission, failed to identify two-thirds of the attacks with an ultimately complicated or fatal outcome. Alternative methods for predicting outcome soon after admission to hospital have included discriminant analysis and Ranson and Pasternack were correctly able to identify 89 per cent of 300 patients retrospectively, using seven variables recorded on admission[10] Prospective assessment of discriminant analysis on a further group of patients would be expected to be less accurate and has not been reported Diagnostic peritoneal lavage[11] provides another means for the early prediction of outcome in acute pancreatitis but owing to the invasive nature of this examination it has not found widespread acceptance outside clinical trials. Thus APACHE II may prove to be a useful addition to the management and study of these patients, providing an objective indication of the severity and possible outcome of an attack soon after admission to hospital; thus, it may permit the early, non-invasive selection of patients for intensive therapy or study in clinical trials.

The peak APACHE II score provided a higher diagnostic accuracy, equivalent to that of the illness-specific scoring systems, although then incurring a similar delay. APACHE II performed as well as the established scoring systems for attacks associated with gallstones but less well for attacks associated with alcohol where the Ranson scoring system (which was derived using data from a predominantly alcoholic patient population) performed particularly well Using the peak APACHE II score, patients could be graded according to their percentage risk of major morbidity or death as has previously been shown for an increasing Ranson score[12].

While the standard illness-specific scoring systems provide a single 'one-off' prognostication the APACHE II score can be repeated daily to monitor the course of the attack. Patients dying within the first 4 days of admission typically showed a rising score reflecting their deteriorating organ function, whereas patients with an uncomplicated or complicated outcome who survived demonstrated falling scores during the first 7 days of their illness with resolution of the systemic manifestations of the attack The APACHE II score appeared to reflect any continuing disease activity and its most useful application in the future may prove to be in monitoring the course of the illness and response to therapy.

Several components of the APACHE II scoring system contributed to the total score in only a few patients and other parameters failed, when considered independently, to provide significant discrimination between the patient groups (*Table 4*). Other potential drawbacks of the APACHE II score, when used to monitor the course of the illness, included scoring patients who were clinically well during the latter half of their hospital stay for a low normal heart rate or an abnormal bicarbonate level (used if P_{O_2} was not available). Perhaps the scoring system might be improved by placing less weight on low normal values in an otherwise well patient. Nevertheless, with the proliferation of illness scoring systems reported, it is an attractive concept to have a single scoring system applicable to all illnesses, and applicable both on admission and throughout the course of the illness.

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Gallstone clearance: a randomized study of extracorporeal shock wave lithotripsy and chemical dissolution

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Following extracorporeal shock wave lithotripsy it is not known whether gallstone fragments are cleared from the gallbladder without the use of oral dissolution therapy. To assess the efficacy of lithotripsy and dissolution therapy, alone or in combination, 35 patients were randomized to one of three treatment groups: lithotripsy alone, dissolution therapy alone or combined lithotripsy and dissolution therapy. All patients had symptomatic gallstones, functioning gallbladders and comparable stone profiles. Lithotripsy was administered using a piezoelectric lithotripter. Dissolution therapy consisted of combined bile acid and terpene. Clearance was assessed at 6 months using ultrasound and oral cholecystography. Patients with less than 50 per cent stone clearance at the end of 6 months were considered failures. The number of patients with total or partial clearance in the combined group (7/10) was significantly greater than those in the lithotripsy alone group (0/10, $P<0.002$). Gallstone clearance following lithotripsy appears to be dependent upon dissolution therapy.

Keywords: Extracorporeal shock wave lithotripsy, bile acid, terpenes

Clearance of gallstone fragments after extracorporeal shock wave lithotripsy should be achieved by mechanical ejection during gallbladder contraction or by dissolution of fragments in surrounding bile.

In 1986 Sackman *et al.* reported initial experience with extracorporeal gallstone lithotripsy and subsequently confirmed the possibility of clearing gallstones in a selected group of patients using extracorporeal lithotripsy and bile acid therapy[1,2].

These results were encouraging but the relative efficacy of lithotripsy and bile acids in their patients was unclear. The Munich group treated patients with both modalities when they would have been considered suitable candidates for bile acid therapy alone[3] Bile acid therapy had a major influence in that only 30 per cent of all their patients achieved complete stone clearance at 2 months following lithotripsy whereas the corresponding figure at 18 months was 93 per cent[2].

In this study the part played by lithotripsy and dissolution therapy; alone or in combination, was examined to establish whether gallstone fragments following lithotripsy could be cleared without the use of oral dissolution therapy, and whether the combination of the two treatments was better than either treatment alone.

Patients and methods

Thirty-five patients (eight men, 27 women) with a mean age of 48 years (range 30–76 years) were studied from January 1988 Patients were selected if they met extended selection criteria as previously reported[4] (a) symptomatic gallstone disease, (b) radiolucent stones of any size or number; (c) radio-opaque stones 3 cm or less; and (d) a functioning gallbladder on oral cholecystography

All patients had suffered at least one attack of biliary colic Lithotripsy treatment was not given if patients were pregnant, had documented peptic ulcer disease, had haematological disorders, were on anticoagulant therapy or if they had suffered complications of gallstones (jaundice or bile duct stones, acute cholangitis, acute pancreatitis or acute cholecystitis)

Patients were randomized into three groups lithotripsy alone, dissolution therapy alone and the combination of lithotripsy and dissolution therapy. Random numbers were generated on an IBM (Portsmouth, UK) personal computer using statistical software (Statgraphics, Statistical Graphics Corporation, Rockville, Maryland, USA)

Four patients were excluded from the study (two from the group receiving lithotripsy alone, one from the group receiving lithotripsy and dissolution and the last from the group receiving dissolution alone) because one failed to return after the first treatment, one became pregnant and lithotripsy was abandoned in two patients because of difficulty of visualization of the gallbladder

Dissolution therapy consisted of a bile acid and terpene preparation[3] Two bile acids were administered in a single tablet form (Lithofalk, Dr Falk Pharma GmbH, Freiburg, FRG), giving approximately 7 mg/kg/day each of chenodeoxycholic acid and ursodeoxycholic acid. The terpene preparation was given as one capsule of Rowachol® (Rowa Pharmaceuticals, Bantry, Ireland) three times a day Terpenes enhance gallstone dissolution when given in combination with bile acids and may also have an antispasmodic effect reducing the episodes of biliary colic during dissolution therapy[5–7]

Lithotripsy was carried out using the EDAP LT-01 piezoelectric lithotripter (Marne la Vallée, France) and all treatments were carried out as outpatient procedures Ultrasound was used to focus the beam of shock waves on the target gallstones within the gallbladder Each patient received 6000 shock waves per treatment session with a maximum of six treatments at 2–3-weekly intervals. The shock waves were administered at a frequency of 2 5 shock waves/s and 100 per cent power

All patients were followed monthly for 6 months for clinical and ultrasonographic assessment Two consecutive monthly ultrasounds and an oral cholecystogram were required to establish total gallstone clearance. Patients were classified into three groups at 6 months. those who had no demonstrable stones, those with greater than 50 per cent clearance (fragmentation with significant clearance of the gallstone mass) and failures (insignficant clearance of the gallstone mass).

Statistical analyses was performed using Fisher's exact test

Results

Of the 31 patients studied, ten received oral dissolution therapy only and shock wave lithotripsy was performed on 21 patients in a total of 69 treatment sessions Twenty-eight lithotripsy sessions were required for the ten patients who received both treatments and 41 sessions for the 11 who received lithotripsy only. Patients required an average of three treatments but this ranged from 1–6 sessions. Successful fragmentation was achieved in all but one patient receiving lithotripsy with an end fragment size of approximately 4 mm.

Although the stone profile in the three treatment groups was not the same, there was no statistical difference comparing the stone size and number as demonstrated in *Table 1*. Three patients had radio-opaque stones (one in the lithotripsy group and two in the lithotripsy and dissolution therapy group). Two of these patients had stones with a calcified core and the third had a stone with a calcified shell.

Seven of ten patients achieved total or greater than 50 per cent clearance of the original stone load in the lithotripsy and dissolution group, whereas only two out of ten achieved this amount of clearance with dissolution therapy alone and none of the ten patients in the lithotripsy only group achieved such clearance (*Table 2*).

All patients with calcified gallstones achieved successful fragmentation but only one patient in the combination group achieved complete clearance of the fragments following lithotripsy. Although more patients were cleared of gallstones in the group receiving the combined therapy, the results only achieved significance ($P<0·002$) when the combination treatment was compared with lithotripsy alone (*Table 2*).

Lithotripsy was well tolerated by most patients. Seven of the 31 patients suffered an attack of biliary colic during the course of their treatment (four in the lithotripsy group, two in the lithotripsy and dissolution therapy group and one in the dissolution therapy group). In those patients receiving lithotripsy, the majority of attacks occurred within 48 h of treatment but none had clinical or biochemical evidence of acute pancreatitis, skin ecchymosis or haematuria.

Table 1 *Stone profile of the patient in each treatment group*

			Stone number		
Treatment group	*n*	Stone size, cm	1	2–3	>4
Lithotripsy	11	1·6(0·34)	2	3	6
Combination	10	1·45(0·28)	3	3	4
Dissolution	10	0·95(0·24)	1	0	9

Values in parentheses are mean(s.e.m.)

Table 2 *Stone profile and treatment outcome of each patient in the treatment groups*

Treatment group	Stone size, cm	Number	Lucent	Clearance
Lithotripsy alone	1·5	2–3	Yes	Failure
	0·5	>4	Yes	Failure
	0·5	>4	Yes	Failure
	1·0	>4	Yes	Failure
	1·5	>4	Yes	Failure
	3·5	1	Yes	Failure
	3·5	1	Yes	Failure
	2·0	>4	Yes	Failure
	3·0	2–3	Yes	Failure
	1·0	>4	Yes	Failure
	1·0	2–3	No	Failure
Lithotripsy and dissolution	2·0	1	Yes	100%
	0·5	>4	Yes	100%
	2·0	1	Yes	100%
	0·5	>4	Yes	100%
	2·0	2–3	No	100%
	3·0	2–3	Yes	>50%
	2·0	1	Yes	>50%
	1·5	2–3	Yes	Failure
	0·5	>4	No	Failure
	0·5	>4	Yes	Failure
Dissolution alone	0·5	>4	Yes	100%
	0·5	>4	Yes	50%
	0·5	>4	Yes	Failure
	0·5	>4	Yes	Failure
	3·0	1	Yes	Failure
	1·0	>4	Yes	Failure
	1·0	>4	Yes	Failure
	0·5	>4	Yes	Failure
	1·0	>4	Yes	Failure
	1·0	>4	Yes	Failure

Discussion

Successful gallstone fragmentation has been reported using shock wave lithotripsy[1,2,8,9]. There are currently several different extracorporeal lithotripters being manufactured and these machines often have very different specifications[10]. The EDAP LT-01 lithotripter employs a piezoelectric system in which shock waves are generated from ceramic crystals and focused on a small target area. This necessitates accurate localization but less pain is produced and the potential for tissue damage to surrounding structures is reduced[8]. This allows this type of lithotripter to be used safely as an outpatient procedure and at more than one treatment session.

Lithotripsy stone fragmentation is the first step and fragment clearance is the ultimate aim of treatment. Ninety per cent of fragments clear the urinary tract within 3 months of renal stone lithotripsy. Gallbladder stone fragments, however, appear to require 12–18 months to achieve a 90 per cent clearance[2]. Sackman *et al.*, who reported these initial results with gallstones, used a bile acid combination as adjuvant therapy. The rationale for this combination was based on an *in vitro* study where gallstone dissolution was shown to be significantly accelerated following fragmentation with lithotripsy[11]. This study suggested that the ideal fragment size after lithotripsy was 2 mm or less. Although particles of this size can be achieved under optimal conditions *in vitro*, clinical localization of the stones may be difficult and larger fragments may remain in the gallbladder after shock wave application.

Sackman *et al.* selected patients for combination therapy with lithotripsy and bile acids in order that they might have the best chance of success[2]. More than 70 per cent of their patients were considered unsuitable for this form of treatment. In many cases this was because of gallstone characteristics. We have, however, shown that it is possible to extend the scope of lithotripsy and dissolution therapy to a wider group of patients and it is these criteria that we have employed in this study[4] This approach will produce a substantial number of treatment failures initially but allows treatment to be offered to more patients It also identifies those patients who are not going to be suitable for the combined treatment.

Patients with residual fragments in the gallbladder can be treated with bile acids but this adds considerably to the cost of the treatment. Mechanical ejection may have a significant effect on fragment clearance. This ejection would depend on the size of the fragments in relation to the cystic duct diameter and the contractility of the gallbladder. Contractility itself appears to be impaired in patients with gallstones but this does not appear to be further impaired by lithotripsy[12].

The majority of the gallstones in the patients receiving dissolution therapy only were small and multiple. The consequence of having smaller stones in this group should have improved the results further but dissolution therapy had little impact when used alone because of the short follow-up of 6 months. The addition of lithotripsy appears to have improved the effect of the combination of bile acids and terpenes. This specific combination of oral gallstone solvents has not been reported by others but it has been found to be satisfactory and well tolerated

This study suggests that mechanical ejection plays little part in emptying the gallbladder of fragments and lithotripsy must be combined with dissolution therapy to achieve effective clearance. No patient receiving only lithotripsy achieved significant clearance of their gallstone mass. This interpretation of the data requires some caution because the numbers studied were small and the gallstone characteristics in each group were not matched.

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Gallbladder surgery following cholecystlithotripsy: suggested guidelines for treatment

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Twenty-three of 229 symptomatic patients undergoing cholecystlithotripsy underwent surgical intervention: 22 of the patients had cholecystectomy performed (five also undergoing choledochotomy) and one patient had a cholecystostomy. Of these 23 patients, five were lithotripsy failures, five developed acute pancreatitis, one had acute cholecystitis, and one had cholangitis. One patient had her gallbladder removed incidentally at the time of surgery for a bleeding gastric ulcer. Ten patients underwent surgery for recurrent biliary pain, probably related to fragment passage via the cystic duct. We suggest that up to 16 of these 23 patients did not necessarily require cholecystectomy, i.e. five patients with pancreatitis, one patient with cholangitis and ten patients with recurrent biliary colic. Conservative and/or endoscopic management may be successful in the first instance to allow further treatment with lithotripsy in the majority of patients. If, however, the expertise to perform endoscopic sphincterotomy is not available or the patient declines further lithotripsy, then resort to surgery may be necessary. We propose that it is the responsibility of the management team in charge of the lithotripsy unit to inform both the patient and the referring clinicians of the possible side-effects and outcome of treatment in an attempt to avoid unnecessary surgical procedures.

Keywords: Biliary lithotripsy, complications, cholecystectomy

There are several means available for the non-operative treatment of gallstones, all of which are currently under investigation. Biliary extracorporeal shock wave lithotripsy (ESWL) is the least invasive method of treating gallbladder stones and is becoming widely available in both Europe and North America. Long-term follow-up, i.e. for more than 12 months, is not yet available in most centres Cholecystectomy remains the gold standard, especially in young, fit, symptomatic patients, and has an overall operative mortality rate of less than 1 per cent[1], which increases to 2 per cent in patients aged over 65 years[2] and is possibly higher, depending on risk factors[3]. As yet there have been no reports of deaths attributable to cholecystlithotripsy. Two other major advantages of this form of treatment are that the vast majority of patients can be treated as outpatients and an extended period of convalescence is not necessary Some patients, however, will require surgery following cholecystlithotripsy. Our objective was to analyse those patients undergoing surgery and to suggest possible guidelines for the treatment of side-effects and complications following ESWL so that unnecessary surgical procedures are avoided or at least deferred

It is apparent that not all gallstone patients are suitable for treatment with ESWL. Currently, most protocols limit patient selection to those with symptomatic radiolucent stones with a maximum size of 30 mm, a maximum of three stones, and a 'functioning' gallbladder on oral cholecystography To date, the Munich group reports the longest follow-up of patients treated by ESWL They report a gallstone fragment clearance rate on actuarial analysis of up to 95 per cent with a follow-up time of between 18 and 24 months when lithotripsy is combined with the use of adjuvant oral chemolitholysis[4]. However, they are only treating between 15 and 25 per cent of patients referred, due to their strict entry criteria.

In Vancouver we have broadened the selection criteria to include a greater number of patients such that up to 50 per cent of symptomatic patients referred to our department are eligible for treatment. Patients with calcified stones as seen on plain radiographs are not excluded. Unlike other groups, we do not use any oral chemolitholytic agents so that clearance of gallstone fragments is by gallbladder expulsion rather than by dissolution. Our broader selection criteria are as follows: (a) minimum stone size of 5 mm with no maximum size; (b) a maximum number of six stones; and (c) a minimum of 20 per cent gallbladder contractility on ultrasonography following a fatty meal to assure patency of the cystic duct.

Contraindications are as follows: (1) abnormal liver function tests; (2) abnormal coagulation studies; (3) acute pancreatitis; (4) acute cholecystitis; (5) the presence of bile duct stones; and (6) pregnancy.

Patients and methods

Between October 1987 and November 1989, we treated 229 patients with symptomatic gallbladder stones using the overhead module of a Lithostar Plus (Siemens, Erlangen, FRG) This module uses ultrasound for targeting gallbladder stones and produces shock waves of greater power than the fluoroscopically guided undercouch module of a standard Siemens Lithostar. Thirty out of 229 patients (13 per cent) had calcified stones as seen at plain abdominal radiography There were 155 women and 74 men with an age range of 20–86 years (mean 55 years) Stone sizes ranged from 5 to 39 mm (mean 17 mm). Treatment sessions were repeated until fragment size was $\leqslant 3$ mm. A maximum of 20 000 shocks or a total number of six lithotripsy sessions was given The mean number of sessions was 2·7 (range 1–6) and the mean number of shocks administered was 10 700 A maximum of 4000 shocks was given per treatment session No patient required general or epidural anaesthesia. Eighty-six per cent of patients required neuroleptanaesthesia using a mixture of intravenous fentanyl and Diazemuls® (KabiVitrum Canada, Inc, Newmarket, Ontario, Canada), and/or transcutaneous electrical nerve stimulation, thus allowing all patients to be treated on an outpatient basis.

The records of all 229 patients were reviewed to ascertain the number of surgical or endoscopic procedures performed, such as endoscopic sphincterotomy, cholecystostomy, cholecystectomy or bile duct exploration Those patients whose records were not up to date or in whom a recent follow-up ultrasonography report was not to hand were contacted directly

Results

Twenty-three of 229 patients (10 per cent) underwent surgery following cholecystlithotripsy with a follow-up time of 2–26 months (mean 10 months) Twenty-two patients underwent cholecystectomy, together with bile duct exploration in five, and one patient underwent cholecystostomy under local anaesthesia No endoscopic sphincterotomies were performed. In five of the 23 patients the gallstones had been successfully fragmented and the patient had completed cholecystlithotripsy treatment; the other 18 patients underwent surgery before a gallstone fragment size of 3 mm or less had been achieved.

The reasons given by the surgeon for performing surgery on these 23 patients were as follows:

1. Acute pancreatitis in five patients. These attacks occurred within 6 days of treatment in two cases and between 4 and 13 weeks in the other three cases. Two patients had partially fragmented calcified gallstones
2. Acute cholecystitis in one patient, which occurred 8 months after successful lithotripsy fragmentation.
3. Cholangitis in one patient, which occurred 1 week after treatment
4. One patient had cholecystectomy performed at the time of gastrectomy for an acutely bleeding gastric ulcer.
5. Recurrent biliary pain in ten patients, including five patients who had undergone successful fragmentation, i.e fragment size $\leqslant 3$ mm.
6. Failure to fragment gallbladder stones adequately in four patients despite the maximum number of 20 000 shocks or a maximum of six lithotripsy sessions One patient had partially fragmented calcified gallstones. Two were asymptomatic and declined further treatment and one patient was undergoing therapy with methyl tert-butyl ether
7. Difficulty in targeting gallbladder stones in one patient.

Early surgery was performed, i.e. during the initial hospital admission, in three out of five patients with acute pancreatitis and in the one patient with cholangitis. Cholecystectomy was delayed for 6 and 18 weeks in the other two patients with pancreatitis and for 4 weeks in the patient with acute cholecystitis. Elective surgery was performed up to 47 weeks after the last lithotripsy session in the remaining 16 patients.

The surgical findings were as follows:

1. All 23 gallbladders contained gallstone fragments, five with fragments $\leqslant 3$ mm.
2. A thickened gallbladder wall was noted in ten patients.
3. A completely normal macroscopic appearance of the gallbladder was noted in eight patients.
4. Local adhesions around the gallbladder were present in eight patients.
5. Petechial serosal haemorrhages were seen in four patients.
6. Stone fragments were found in the common bile ducts of three patients, two of whom had a preoperative diagnosis of acute pancreatitis and one a diagnosis of biliary colic
7. Histological examination of the 22 excised gallbladders revealed changes due to chronic cholecystitis in all cases. In addition, four gallbladders demonstrated features of acute inflammation superimposed on the underlying chronic inflammatory changes. One gallbladder also showed features compatible with cholesterolosis. One of four gallbladders excised within 1 week of lithotripsy treatment demonstrated epithelial erosions, possibly due to the effects of recent shock wave treatment Another patient demonstrated mucosal scarring in a gallbladder which was excised 38 weeks after lithotripsy treatment.

After recuperation from surgery all patients were contacted to assess clinical outcome and their satisfaction with lithotripsy. Personal replies were obtained from 20 of the 23 patients. Most patients (14 out of 20) were not dissatisfied with their lithotripsy treatment despite having a good result from surgery. At least three patients were encouraged by their general practitioner to undergo surgery due to the presence of persisting gallstone fragments on follow-up ultrasonography and recurrent right upper quadrant pain. These patients had not completed their full lithotripsy treatment and, if so encouraged, would have continued to do so. Five patients would, in hindsight, have chosen surgery as a first option. One of the 20 patients questioned continued to have abdominal pain 2–3 months after cholecystectomy which raises the important question of whether the correct diagnosis was made in the first instance

Discussion

Cholecystlithotripsy remains under evaluation. The outcome is being closely monitored by most clinicians interested in this field. Cholecystectomy, however, still remains the gold standard for the management of uncomplicated gallstones, especially in younger patients. To date, the reported incidence of cholecystectomy following biliary lithotripsy varies from 1·0 to 8·1 per cent[4–10]. Most of these patients underwent surgery for persistent biliary colic However, data regarding the indications for surgery following cholecystlithotripsy are scarce

The high incidence of surgery (10 per cent) reported in our series may be due to a variety of reasons One factor is that in Vancouver we do not use any oral chemolitholysis either before or after cholecystlithotripsy, thus relying on mechanical ejection to clear small fragments from the gallbladder This has resulted in a more rigorous treatment protocol, often requiring multiple lithotripsy sessions to achieve successful fragmentation to a size of $\leqslant 3$ mm All patients, however, can be treated on an outpatient basis. We initially reported a 29 per cent fragment clearance rate at 4 months[11] and this has increased to 61 per cent at 12 months in 136 patients who have undergone successful fragmentation[12]. These figures are comparable with those obtained in centres using routine adjuvant oral chemolitholysis with either ursodeoxycholic acid or a mixture of chenodeoxycholic and ursodeoxycholic acid[4,6–8] We believe the use of these agents is not as yet of proven value, and further randomized controlled studies should help to clarify their effectiveness[9].

Another factor is a natural preference to perform cholecystectomy by many of the referring surgeons outside the main treatment centre when an instant 'cure' has not been achieved by lithotripsy This may be related to the lack of data on the long-term sequelae of biliary lithotripsy with a failure to pass on relevant information regarding side-effects and complications of such treatment to the patient and referring clinician Undoubtedly some patients will not be sufficiently motivated to continue with repeated lithotripsy sessions, especially if they are suffering repeated attacks of biliary colic. We would recommend that a letter is sent to both the referring clinician and given to the patient indicating that biliary pain or colic following cholecystlithotripsy is to be expected in up to 58 per cent of patients[4,8], and is often an indicator of the passage of small fragments. In our series, 23 per cent of patients developed biliary colic, half of whom required some form of over-the-counter or prescription analgesia[12] If symptoms or signs of acute cholecystitis are present, then surgery is the treatment of choice, and this has a reported incidence of <1 per cent in most lithotripsy series. Other side-effects that may occur include transient macroscopic haematuria in 3–5 per cent of patients and minor skin petechiae in up to 80 per cent. The only other complication that has occurred following cholecystlithotripsy was a subcapsular hepatic haematoma which was managed conservatively[13].

The incidence of pancreatitis following biliary lithotripsy is quite low in our series (2 per cent) and in other reports is said to occur in 1–2 per cent of patients treated[7,8]. The management of these patients is more controversial and is not at all clear at the present time. The incidence of' hyperamylasaemia is possibly greater, but most patients with less severe abdominal pain will not generally have their serum amylase level evaluated. A recent report by Heberer *et al.*[10] described five cases of pancreatitis following cholecystlithotripsy in which only one patient required endoscopic sphincterotomy. The remaining patients were managed successfully without further intervention. We also suggest that patients with documented acute pancreatitis could be managed conservatively in the first instance with subsequent retreatment by ESWL of any remaining fragments >3 mm in size, provided that the bile ducts are clear If symptoms and signs fail to subside then early endoscopic retrograde cholangiopancreatography (ERCP) and sphincterotomy with stone extraction have been shown to reduce morbidity and hospital stay[14]. This form of management may be unacceptable to many surgeons due to the known high incidence (up to 63 per cent) of recurrent acute pancreatitis in patients who have had one previous episode of proven gallstone pancreatitis. They would advocate cholecystectomy during the same hospital admission as the episode of acute pancreatitis, with bile duct exploration where stones have been demonstrated[15,16]. Surgery performed during the acute attack when the serum amylase level remains elevated is associated with a high mortality rate of 31 per cent, whilst if delayed until the serum amylase level returns to normal, the mortality rate is reduced to 2 per cent[17].

In our series, all five patients who developed acute pancreatitis underwent cholecystectomy; three were dealt with during the same hospital admission and two were operated on electively. Bile duct exploration for stones was necessary in two patients. Only two patients had a successful ERCP without sphincterotomy before surgery, which in one case showed the presence of stone fragments. Of the other three patients, one had an attempted ERCP which failed due to the presence of a large hiatus hernia One patient had a non-functioning gallbladder on a ^{99}Tc-Sn-2,6-diethylacetanilidoiminodiacetate (HIDA) scan, and ERCP was thought not to be necessary as this finding on scanning was interpreted as an indication for surgery The other patient had surgery performed in an outlying hospital where suitable endoscopic expertise was not available.

We suggest that up to 16 of our 23 patients may not have necessarily required surgery following biliary lithotripsy under our existing guidelines, while in one patient in whom cholecystectomy was performed, the original symptoms persist. The main argument against cholecystlithotripsy is that the diseased organ is left *in situ* with a predicted gallstone recurrence rate of up to 50 per cent[18,19] Of 45 patients in our unit followed up by serial ultrasound examination for an average of 10 months, six (13 per cent) have developed recurrent stones although only two of these patients are symptomatic. It has been shown that up to 80 per cent of gallstones may remain asymptomatic, thus not necessarily requiring further treatment[20].

A further, overstated, argument is that some patients may develop gallbladder carcinoma in later life, but clinically this appears to be a rare cause of death. However, cholecystlithotripsy does appear to be an extremely safe procedure with no reported mortality. In two of our patients undergoing cholecystectomy there were mucosal changes, probably due to the effects of lithotripsy treatment. In one case epithelial erosions were noted in a gallbladder excised 1 week after lithotripsy, and in the other mucosal scarring was seen in a gallbladder excised 38 weeks after treatment. In neither case were the changes thought to be clinically significant. This adds further evidence in favour of the overall safety and efficacy of gallstone treatment with extracorporeal shock waves

We recommend that there should be a multidisciplinary team approach to the management of patients with gallbladder stones, the team including a surgeon, a gastroenterologist and a radiologist. It is the duty of this team not only to assess the suitability of patients for treatment but to provide adequate information regarding the overall treatment programme, results and management of possible complications to both the referring clinicians and their patients With better communication it may be possible to avoid some unnecessary surgical procedures. Some patients will nevertheless continue to be swayed by the experience of their referring clinician. It is important that patients must be sufficiently motivated to complete the full lithotripsy treatment programme especially if multiple sessions are required, otherwise the outcome of such treatment will inevitably be disappointing. Further long-term evaluation of ESWL for gallstones is necessary to determine which patients are most suitable for treatment, and to determine the long-term incidence of fragment clearance, side-effects and stone recurrence rates. Patients now have a choice between surgery and other forms of non-operative treatment of which cholecystlithotripsy is the most widely available.

ESWL may become the treatment of choice in the elderly, high-risk population with symptomatic gallbladder stones. The 10 per cent incidence of surgery following cholecystlithotripsy in our series is the highest yet reported, for the reasons discussed. We suspect that other groups performing ESWL for gallstones will refer more patients for surgery as follow-up times become longer. However, early results are encouraging although more data are required to satisfy the needs of both clinicians and patients.

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Case report

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Treatment of sleep apnoea by vertical gastroplasty

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Obstructive sleep apnoea is predominantly due to excessive body-weight, and in particular excessive fat in the neck[1,2]. It is likely that this excessive weight in the neck both compresses the upper airway at rest[3] and adds an extra compressive load when the pharyngeal dilator muscle tone is partially withdrawn at sleep onset[4]. Both these factors conspire to provoke pharyngeal collapse during sleep – obstructive sleep apnoea (OSA). Weight loss can thus be curative[5]. However, several factors make it difficult for overweight patients with OSA to lose enough weight to stop the obstructive apnoeas. The sleep deprivation of OSA may provoke hyperphagia[6], the hypersomnolence reduces physical activity and saps the willpower to diet. It is also likely that years of heavy snoring (a hallmark of OSA) may damage the pharynx, making it more 'floppy'[7]. Thus, it may be necessary, in order to cure the sleep apnoea, to go down to a lower weight than that at which the problem originally began to occur. This case report describes the use of vertical Silastic® ring (Dow Corning, Reading, UK) gastroplasty to produce substantial weight loss in a man with severe OSA

Case report

A 41-year-old man presented with severe daytime hypersomnolence and loud snoring. The hypersomnolence had led to car accidents and poor work performance. His current weight was 160·9 kg with a height of 173 cm, thus the body mass index was 54 kg/m^2. Some years previously (before the onset of hypersomnolence) he had lost 64 kg over 6 months but had soon regained it all. He had a history of mild asthma, managed with salbutamol rotacaps as required Apart from the obesity physical examination, particularly of the nose and throat, was normal His neck circumference was 55·5 cm, 137 per cent of normal predicted from height

Overnight sleep studies revealed gross sleep apnoea with 40 apnoeas per h (324 over the whole night) and recurrent falls in percentage oxygen saturation (Sa_{O_2}) down to a minimum of 35 per cent (*Figure 1a*). These apnoeas occurred regardless of posture. Nasal continuous positive airway pressure (NCPAP) treatment was introduced at night[8] with complete resolution of the apnoeas and daytime symptoms (*Figure 1b*) Other routine investigations confirmed the gross simple nature of his obesity. The patient wished to stop NCPAP therapy and massive weight loss seemed the only option, since he considered tracheostomy unacceptable

On 4 July 1988 he underwent vertical Silastic ring gastroplasty[9]. There was 8 cm of abdominal fat but no hiatus hernia or gallstones. The visibly fatty liver was biopsied and subsequent report showed mild to moderate fatty change. The stomach was stapled using a TA 90 BN (AutoSuture, Ascot, UK) stapler to create a 50 ml proximal compartment. This size was measured accurately by an inflatable balloon passed into the stomach by the anaesthetist. The stoma, 1 2 cm in diameter, was reinforced circumferentially by a 5 cm Silastic band held in place by a polypropylene suture (*Figure 2*).

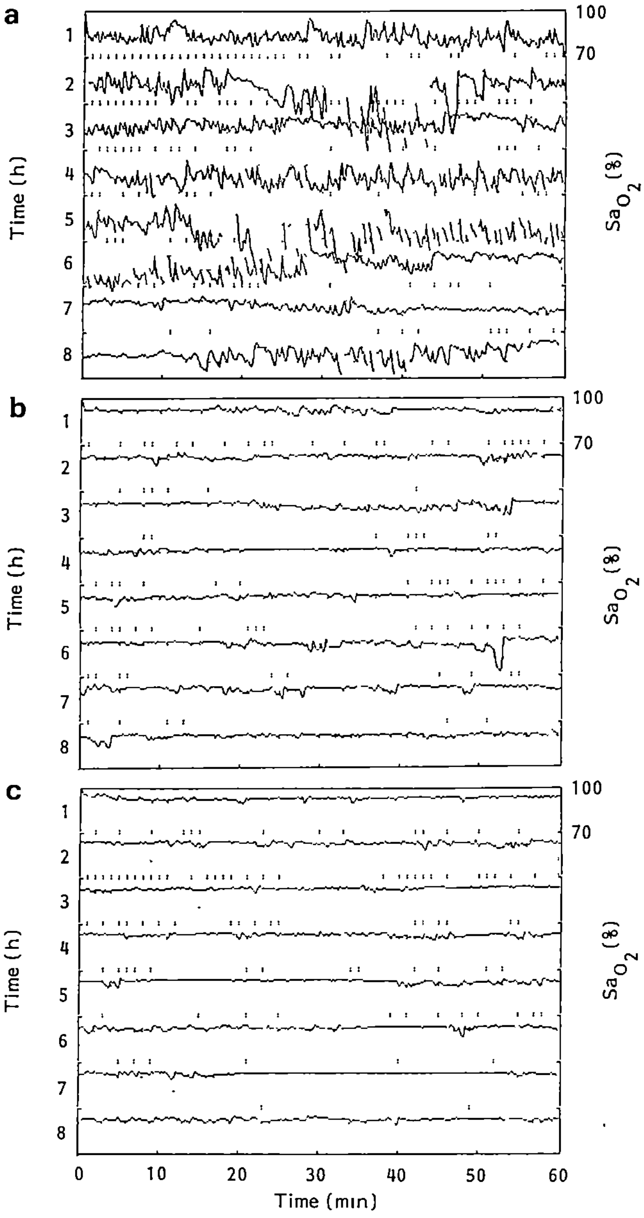

Figure 1 *Eight hours of overnight oximetry – continuous tracing (OHMEDA, Harlow, UK 3700 – flexprobe)* **a** *Overnight sleep study before surgery,* **b** *sleep study using nasal continuous positive airway pressure treatment,* **c** *sleep study 4 months after operation* Sa_{O_2}, *oxygen saturation*

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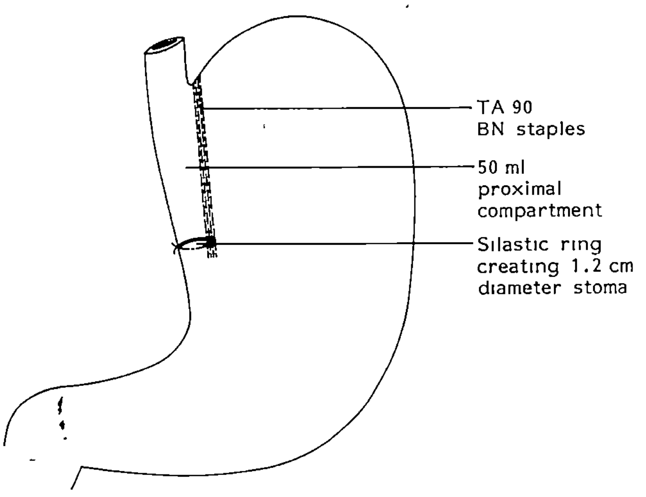

Figure 2 *Vertical Silastic ring gastroplasty*

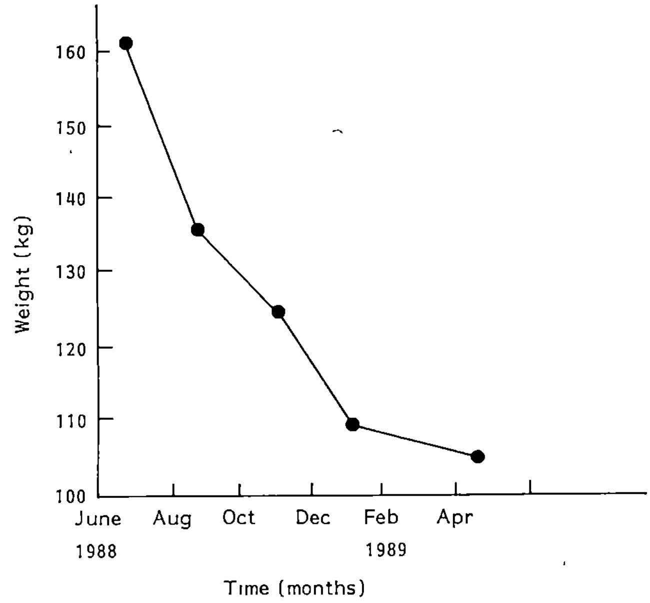

Figure 3 *Weight loss after surgery (June 1988) until April 1989*

After operation he was managed in the intensive care unit for 24 h Little analgesia and no opiates were given He used NCPAP during periods of sleep By the third postoperative day he was taking free fluids Ten days after operation he was discharged, the wound having healed well A limited barium meal showed little hold up at the stoma which was of the usual size (1·2 cm diameter), the proximal compartment emptying satisfactorily For 6 weeks he had a 500 kCal fluid diet with protein supplement, before the gradual re-introduction of solid food

His postoperative weight reduction is shown in *Figure 3* Six weeks after operation he had a weekend break without NCPAP and without any return of hypersomnolence Three months after operation he had a 2 week holiday without using NCPAP and had no return of daytime hypersomnolence In November 1988 a repeat sleep study confirmed total abolition of obstructive sleep apnoea and snoring (*Figure 1c*) His neck circumference was then 42 cm, 104 per cent of the predicted normal. From then on he no longer used NCPAP He now eats saucer sized meals and has few side effects apart from occasional vomiting due to overindulgence. Hypersomnolence is no longer a problem.

Discussion

This case history illustrates the value of treating the primary problem of obstructive sleep apnoea – massive obesity. Pharyngeal surgery (uvulopalatopharyngoplasty) is an alternative surgical approach with widely varying success rates, both short and long-term. The success rate may depend on how radical the palatal resection is, but ability to predict the success of the operation is poor. Conway *et al.*[10] found that an initial weight below 125 per cent of ideal lessened the chance of success, whereas Riley *et al.*[11] and Guilleminault *et al.*[12] found the opposite, greater obesity reducing success. Riley *et al.*[11] also showed that cephalometry might demonstrate a predominantly hypopharyngeal level of obstruction which also reduced the likely success of pharyngeal surgery.

Uvulopalatopharyngoplasty is not without hazards Because of this and uncertainty about success and whom best to operate on, this operation has not become standard therapy in most centres. Vertical Silastic ring gastroplasty is a relatively safe and simple operation that can cure both OSA and obesity. This operation should be considered more often for obese patients with OSA since they may find it even harder than usual to lose the substantial amounts of weight necessary to cure their condition.

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Surgical presentation of Kawasaki disease (mucocutaneous lymph node syndrome)

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Five patients with Kawasaki disease (mucocutaneous lymph node syndrome) are reported whose varied presentations included acute abdominal pain, peripheral arterial aneurysms, digital gangrene and sterile pyuria and whose presenting pathology ranged from hydrops of the gallbladder to enteric pseudo-obstruction. As the complications of the disease can usually be managed without resort to surgery, which is associated with a mortality rate of up to 25 per cent, the recognition of Kawasaki disease will prevent hazardous and unnecessary laparotomy.

Keywords: Kawasaki disease, conservative treatment

Kawasaki disease (mucocutaneous lymph node syndrome) is a disseminated vasculitis of unknown cause affecting small and (later) large arteries in young children of mean age 2 years; it is very unusual above 6 years. A self-limiting and non-recurrent disease, it was first described by Tomisaku Kawasaki in 1967[1]. Pyrexia for more than 5 days, together with at least four further signs (*Table 1*), is mandatory for diagnosis.

Kawasaki disease is important to general surgeons since a small number of patients may present with gallbladder hydrops, intestinal pseudo-obstruction, ischaemic colitis or cervical lymphadenopathy masquerading as a cervical abscess. Such presentations may obscure the diagnosis and lead to unnecessary surgery.

Patients

Five patients seen in the last 5 years and illustrating various surgical features of Kawasaki disease are presented. They were all initially admitted to medical wards before being referred for surgical opinion.

Case 1

A 6-year-old girl with a 4-day history of painful unilateral cervical lymphadenopathy and fever was admitted for treatment of supposed pyogenic adenitis. On examination she had two tender, hard lymph nodes in the left anterior triangle and a fever of 39°C. Investigations revealed a white cell count of 17×10^9/l (85 per cent neutrophils) and an erythrocyte sedimentation rate of 88 mm/h. Blood cultures were sterile. She was commenced on intravenous ampicillin and flucloxacillin, but over the next few days had a remittent fever and proceeded to develop conjunctivitis, stomatitis, palmar erythema and finger tip desquamation. Serum IgE was 1285 mg/100 ml (normal = 1–180). A diagnosis of Kawasaki disease was made and she was given aspirin. Her condition resolved over the next 10 days.

Case 2

A 16-month-old boy with a 7-day history of fever, irritability, rash, cervical lymphadenopathy and conjunctivitis was admitted to hospital and then went on to develop finger tip desquamation and generalized lymphadenopathy. The serum IgE was grossly elevated. A diagnosis of Kawasaki disease was made. Two weeks after admission he developed abdominal distension and bile-stained vomiting. Abdominal radiographs showed distended bowel loops with fluid levels and a visible gallbladder shadow. He was treated conservatively with intravenous fluids and a nasogastric tube and the intestinal pseudo-obstruction resolved over 48 h.

Case 3

A 3-month-old girl presented with a 3-day history of high fever, diarrhoea, vomiting and an intermittent rash. On examination the only abnormalities were a fever of 40°C and dry red lips. Investigations revealed a white cell count of 7×10^9/l (90 per cent neutrophils) with a left shift. Midstream urine showed sterile pyuria. Septicaemia was diagnosed and penicillin and gentamicin therapy commenced. Over the following 6 days the fever continued and erythema of her mouth and conjunctivae developed. The rash consolidated into a fixed macular form and small cervical nodes appeared. Remittent fevers continued for the following month, but intensive multisystem investigation was unhelpful. She recovered and was discharged, only to return 4 months later after her general practitioner diagnosed a right axillary artery aneurysm. This unusual diagnosis was confirmed by arteriography (*Figure 1*). The aneurysm was excised and replaced with a vein graft. Histological examination of the thickened arterial wall revealed fibrous thickening of the intima, interruption of the internal elastic lamina and chronic inflammatory cell infiltration, all suggestive of healed Kawasaki disease.

Table 1 *Principal diagnostic criteria in Kawasaki disease*

High remittent fever for more than 5 days
Bilateral conjunctival injection
Changes in the mouth (one or more):
  Dry, chapped, fissured, reddened lips
  Strawberry tongue
  Diffuse reddening oral mucosa
Changes in extremities:
  Purple-red discolouration of palms and soles
  Indurated hands and feet
  Later – peeling of skin, initially beneath nails
Erythematous rash after 3–5 days on trunk, extremities and perineum
Cervical lymphadenopathy, usually unilateral and single, in 50–75 per cent

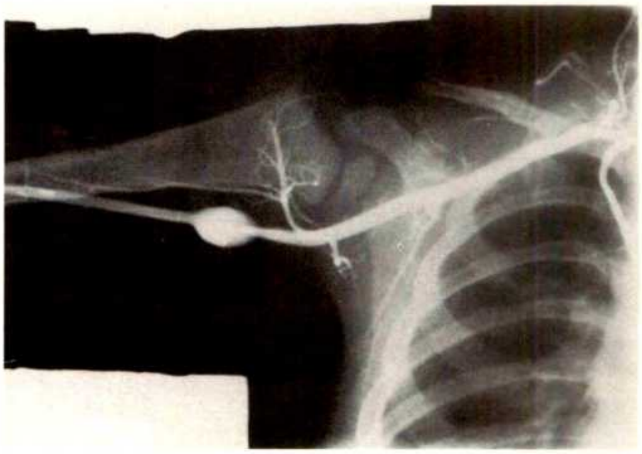

Figure 1 *Transfemoral arteriogram demonstrating an aneurysm of the third part of the right axillary artery*

Table 2 *Reported complications of Kawasaki disease*[7]

Complication	Prevalence (%)
Sterile pyuria	53
Arthropathy	27
Electrocardiographic changes	25
Coronary artery aneurysms	13
Hepatosplenomegaly	8
Pneumonitis	5
Aseptic meningitis	4
Intestinal pseudo-obstruction	3
Hydrops of gallbladder	3

Case 4

A 4-year-old girl was admitted with malaise and painful cervical lymphadenopathy of 8 days duration followed by the development of abdominal pain, sore throat, fever, redness of the eyes, lips and mouth together with a morbilliform rash and peripheral oedema. The day before admission she developed bile-stained vomiting. On examination she was grossly dehydrated with generalized lymphadenopathy and a fever of 40°C. Her abdomen was distended, with peritonism limited to the right upper quadrant. Investigations revealed a neutrophilia of 30×10^9/l, sterile pyuria and a lymphocytic meningitis. Uniform intestinal distension was seen on an abdominal radiograph and ultrasound examination revealed an acalculous hydropic gallbladder. A diagnosis of Kawasaki disease was made and high-dose aspirin treatment started. Her remittent fever continued for 7 days and she suffered desquamation of her finger tips. The abdominal signs resolved completely on medical management, as did the abnormality detected by ultrasound scan. She was discharged after 4 weeks.

Case 5

A 3-year-old boy was admitted with a 3-day history of fever, abdominal pain, redness of eyes and mouth, arthralgia and a rash. On examination he was febrile (40°C), dehydrated and jaundiced with severe conjunctivitis and stomatitis. There was tenderness in the right upper quadrant of the abdomen. Investigation revealed an erythrocyte sedimentation rate of 94 mm/h and an elevated serum IgE. The abdominal ultrasound scan showed an acalculous hydropic gallbladder. A diagnosis of Kawasaki disease was made. The child was treated conservatively with full resolution of the clinical signs and ultrasonic appearances over the next 10 days.

Discussion

It is important for the general surgeon to recognize the features of Kawasaki disease when faced with an 'acute abdomen' with gallbladder distension, intestinal pseudo-obstruction, ischaemic colitis or pancreatitis[2–5], or by a patient with cervical lymphadenopathy which may be misdiagnosed as a cervical abscess. Kawasaki reported a new disease afflicting 50 Japanese children after 1960. This account did not appear in English translation until 1974[6].

A series of 523 patients studied by the Centers for Disease Control in the United States (where all reported cases between July 1976 and December 1980 were reviewed[7]), confirmed the diagnostic criteria (*Table 1*). In this series the five diagnostic criteria were reported in 96 per cent of cases, with the exception of lymphadenopathy which was present in 82 per cent[7]. This high correlation means that even a relatively rare disease[8] should be recognizable when encountered. The present series of five surgical patients in 5 years should be considered in the context of a total of 12 patients seen by the paediatric unit as a whole in the same period. While this is a relatively common disease in Japan and North America, only 196 confirmed cases were reported in the UK between July 1986 and July 1988[9].

These patients are in a poor risk group with respect to operation, with coronary aneurysms in 13 per cent and myocarditis in 25 per cent. Myocardial infarction is the commonest cause of death occurring in 0·5–2 per cent of patients[6,10]. Of the reported complications (*Table 2*), it is the cardiac dysrhythmias and coronary artery occlusion by aneurysms that confer an overall mortality rate of 0·5–2 per cent[6,10] and an operative mortality rate of 25 per cent[2]. The latter figure is derived from a series of only ten patients in Ottawa, of whom four had surgical features and one died, but there are few surgical reports for comparison. These statistics render laparotomy a formidable undertaking, particularly when the usual complications of the disease can be managed without resort to surgery. The recognition of the syndrome and preoperative assessment of the myocardium by electrocardiography and the coronary vessels by Doppler ultrasound studies may qualify any decision to operate.

The conservative management of abdominal complications of Kawasaki disease, particularly regarding the serial ultrasound scanning of gallbladder hydrops, is well documented[11]; it is appropriate provided that the patient does not deteriorate clinically and the gallbladder distension resolves[12]. However, there are situations where deterioration of the patient's condition or progressive development of peritoneal signs necessitates operation. Nevertheless, it is important that the diagnosis of Kawasaki disease be considered as it is a recognizable condition for which laparotomy should be avoided if possible.

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Vastus lateralis myocutaneous flap for reconstruction of defects around the groin and pelvis

We present our experience using the vastus lateralis myocutaneous flap for the repair of defects around the groin and pelvis. It is a relatively new technique, with many advantages over other flaps used in this area, though it has limitations. The history, anatomy and surgical technique of raising the flap are described and clinical cases are discussed. The importance of patient selection is highlighted.

Keywords: Pelvic and groin defects, vastus lateralis myocutaneous flap

The reconstruction of large defects around the groin and pelvis (principally pressure sores) has been greatly facilitated by the development of local myocutaneous flaps. This paper presents our experience of the relatively new vastus lateralis myocutaneous flap, the use of which has not as yet been reported in this country. The repair of trochanteric pressure sores using the vastus lateralis muscle flap was described in 1977 by Minami *et al.*[1]. In 1982 Bovet *et al.*[2] described the vastus lateralis myocutaneous flap and reported favourable results in similar cases. Drimmer and Krasna[3] reported its use in treating decubiti involving the greater trochanter, the ischium and the posterior thigh. The quadriceps musculocutaneous flap, incorporating the vastus lateralis muscle, was described by Larson and Liang in 1983[4], for the repair of hemipelvectomy defects.

Anatomy

The vastus lateralis is the largest of the quadriceps group of muscles, accounting for the major portion of thigh bulk. It functions as a knee extensor and also contributes to the lateral stability of the knee joint. It arises from the posterolateral aspect of the upper femur. Anteromedially, it is adjacent to and continuous with the rectus femoris muscle. The aponeurotic deep surface of the vastus lateralis moves freely over the underlying vastus intermedius muscle. A flat tendon arises on the deep surface of the lower part of the muscle and inserts into the superolateral aspect of the patella and the lateral condyle of the tibia. Innervation is by a branch of the posterior division of the femoral nerve, and its main artery is a large descending branch of the lateral circumflex artery (*Figure 1*). These form a neurovascular bundle which lies a hand's breadth below the greater trochanter. Selective injection studies by Zuffrey *et al.*[5] show the vascular cutaneous territory, supplied via fasciocutaneous branches, extending along the distal two-thirds of the thigh as far as the patella. This observation has been confirmed in our own dissections and those of Swartz *et al.*[6].

Surgical technique

The axis of the vastus lateralis myocutaneous flap is a line drawn on the skin between the anterior superior iliac spine and the upper lateral aspect of the patella (*Figure 2*), marking the plane of dissection between the vastus lateralis and rectus femoris muscles. The primary defect having been debrided, the islanded skin paddle is outlined, beginning inferiorly above the patella with two-thirds of the width anterior to the axis of the flap. This ensures that the skin paddle overlies the vastus lateralis muscle, leaving the fascia lata undisturbed. To allow direct closure of the donor site, the maximum flap width is about 6 cm; the length may extend to 12 cm. Starting high in the thigh, the incision runs along the axis of the flap. The vastus lateralis muscle is identified and, by using blunt dissection, the plane between it and rectus femoris is mobilized. The neurovascular pedicle enters the vastus lateralis medially and runs on the undersurface of the muscle for all of its length. Having identified it at the beginning of the dissection it is protected from inadvertent division in the upper part of the thigh. The small communicating vessels between the muscles are divided as the dissection proceeds. The lateral side of the muscle can be dissected with impunity. Using sharp dissection, working downward from the greater trochanter, the vastus lateralis is separated from it and the vastus intermedius. The surgeon's finger may then be used to push the vastus intermedius apart from the edge of the vastus lateralis, freeing the muscle flap with its isolated skin paddle. When raised, the flap has a wide arc of rotation

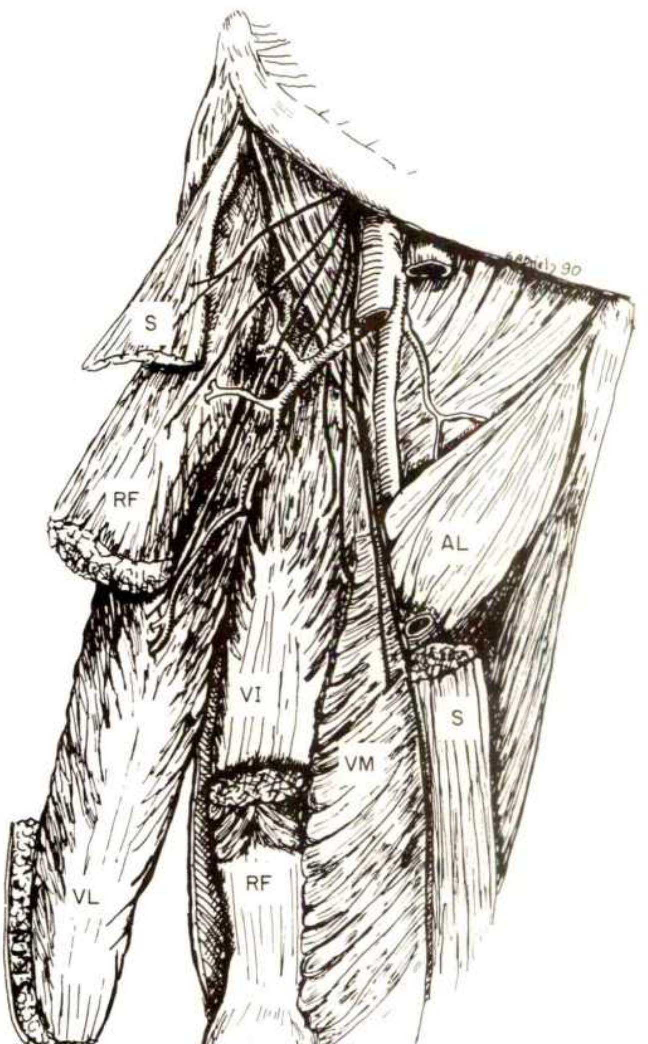

Figure 1 *A diagram showing the sartorius (S) and the rectus femoris (RF) muscles cut away to reveal the lateral circumflex artery branches to the vastus lateralis muscle (VI, vastus intermedius; VL, vastus lateralis; VM, vastus medialis and AL, adductor longus)*

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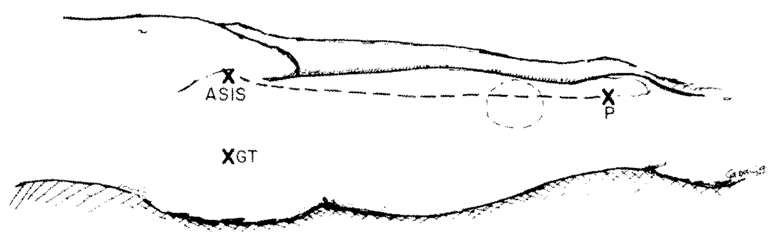

Figure 2 *The axis of the vastus lateralis myocutaneous flap marked, running from the anterior superior iliac spine (ASIS) to the upper lateral patella (P) with the skin paddle outlined, two-thirds of which lie anterior to the axis (GT, greater trochanter)*

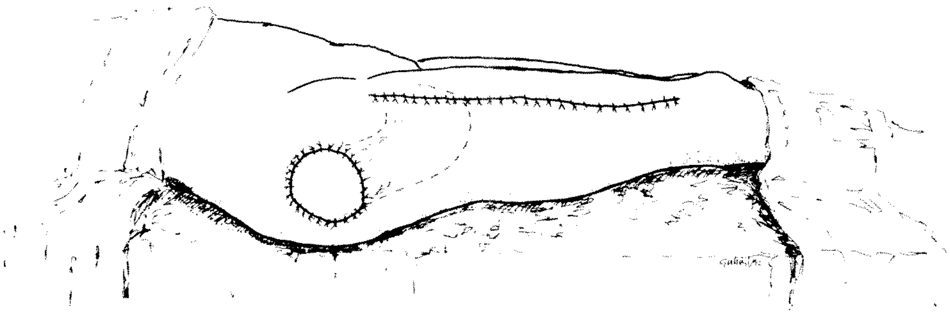

Figure 3 *The vastus lateralis myocutaneous flap tunnelled and inset in the defect remaining after the debridement of a trochanteric indolent pressure sore as in case 1, and the donor defect closed directly*

Table 1 *Details of patients in whom a vastus lateralis myocutaneous flap has been used for reconstruction*

Case	Sex	Age	Medical history	Primary defect	Postoperative stay	Complications
1	F	28	Paraplegic with trochanteric pressure sore	7 × 7 cm	10 days	None
2	M	44	Paraplegic with failed biceps femoris flap for an ischial pressure sore	6 × 8 cm	12 days	None
3	F	67	Trochanteric pressure sore following pneumonia	8 × 8 cm	18 days	None
4	M	65	Groin and iliac dissection including skin for nodal recurrence of penile cancer	12 × 6 cm	21 days	Lymphocele of groin required drainage
5	M	50	Paraplegic with ischial pressure sore after failed surgical and conservative treatment	10 × 6 cm	16 days	Donor site healed after 14 day delay

and can be subcutaneously tunnelled to reach the greater trochanter, the ischium or the groin. The flap is then sutured into the defect and the donor site is closed primarily (*Figure 3*) over a closed suction drain. Details of patients in whom we have used the flap are summarized in *Table 1*.

Discussion

A pressure sore, when excised, leaves a wound with the same characteristics as a compound injury elsewhere, i.e. a defect of skin and soft tissue, exposure of underlying bone and almost universal bacterial colonization and contamination. Godina[7] has shown that success rates in the reconstruction of compound limb defects are higher when flaps that include muscle are used. Vascularized muscle allows prompt healing even in the presence of contaminated wounds. The vastus lateralis is an ideal myocutaneous flap in that it has a reliable vascular pedicle, is easy to dissect, has a wide arc of rotation and is an acceptable donor site. These qualities are not all fulfilled by the myocutaneous flaps more commonly used in the repair of defects around the groin and pelvis.

Though the traditional myocutaneous flap from the lateral thigh is the tensor fasciae latae flap, its reliability has been called into question. The cutaneous perfusion of the artery supplying it extends only to the proximal half of the lateral thigh skin[5]. Therefore the distal extension of the tensor fasciae latae flap, when raised, is deprived of its normal arterial inflow coming medially from the fasciocutaneous arteries of the vastus lateralis, laterally from the posterior compartment septocutaneous branches and inferiorly from the superior lateral geniculate artery[5,8]. The random nature of its blood supply makes the distal portion of the tensor fasciae latae flap prone to inadequate perfusion and necrosis. In contrast the islanded vastus lateralis myocutaneous flap has many advantageous features; it has a potentially large muscle bulk, its arc of rotation is wide, its vascular pedicle is reliable and it produces a functionally and cosmetically acceptable donor site. Even after multiple attempts at treatment of other pressure sores with other local flaps, because of its anatomical location the vastus lateralis segment needed for the myocutaneous flap is normally left undamaged. The vastus lateralis, separated from the fascia lata by loose areolar tissue, presents perforating vessels to the overlying skin at its anterior border above the knee. In its upper two-thirds, particularly laterally, there is a definite surgical plane between it and the vastus intermedius. The vastus lateralis neurovascular bundle is located in fatty areolar tissue, permitting easy dissection. The muscle also has vascular contributions from distal perforators of the superficial femoral artery and the superior lateral geniculate artery, which act retrogradely allowing the muscle to be raised distally to cover the knee joint[6]. As a muscle only flap, it has been described to cover defects in a variety of locations[1,9,10]. Although a very useful development, the muscle only flap has a disadvantage in that it requires cover with a split skin graft. This is avoided with the islanded vastus lateralis myocutaneous flap, which utilizes the same essential technique for freeing the vastus lateralis muscle and provides the same arc of rotation. Our decision to use this flap in an ambulant patient (case 4) was vindicated by his preservation of normal quadriceps function. Swartz *et al.*[6] reported a similar outcome when the vastus lateralis was used as a distally based muscle flap. This series contains the first report of the use of the islanded vastus lateralis myocutaneous flap for repair of a groin defect. The inferiorly based rectus flap is commonly used for such defects, but pre-existing abdominal wall scarring or respiratory disease may prohibit its use.

In conclusion, the islanded vastus lateralis myocutaneous flap is technically simple to raise, reliable in its vascular supply and has a wide arc of transposition. Its donor site is closed directly, is cosmetically acceptable and has a low morbidity. This flap deserves wider application in both plastic and general surgery, with a possible role in the repair of perineal fistulas, groin dissection defects and perianal excisional defects in patients with Crohn's disease.

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Case report

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Massive gastrointestinal haemorrhage due to ileal varices

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Bleeding from 'ectopic' varices outside the gastro-oesophageal region is an uncommon complication of portal hypertension. However, awareness of the condition and its characteristic presentation can enable diagnostic and therapeutic procedures to be performed rapidly with an increased likelihood of a successful outcome. This report describes a patient with massive haemorrhage from ileal varices; the management of this unusual cause of gastrointestinal bleeding is discussed.

Case report

A 72-year-old woman with alcoholic cirrhosis was admitted with hepatic encephalopathy precipitated by gastrointestinal bleeding demonstrated by the passage of dark red blood *per anum*. During the previous year she had required two courses of injection sclerotherapy for bleeding oesophageal varices and had also been admitted with a bleeding duodenal ulcer which responded to conservative treatment. Physical examination revealed stigmata of chronic liver disease and an old lower mid-line scar from a hysterectomy 10 years previously. Endoscopy demonstrated oesophageal varices and a healed duodenal ulcer but no blood in the upper gastrointestinal tract. The patient was initially considered by a medical gastroenterologist to be too ill for surgery. However, with continued bleeding *per anum* emergency angiography was performed. The venous phase of a selective superior mesenteric angiogram revealed venous pooling in the pelvis and two large mesenteric veins (*Figure 1*). Despite these findings embolization was performed because of a suspicious blush in the ileocolic territory during the arterial phase. This failed to control the haemorrhage and, despite the patient's poor condition, a laparotomy was urgently undertaken.

The main operative findings were an adhesion between the ileum and the lateral pelvic wall in the region of an enormously dilated ovarian vein stump and a distal segment of ischaemic small intestine which was thought to have been caused by the radiological embolization. When the intestine was dissected free, large venous lacunae were discovered in the wall of the adherent ileum with two finger-sized veins in the adjacent mesentery. The bleeding ovarian vein was oversewn and a limited ileocolic resection performed with end-to-end anastomosis.

Opening the resected small bowel revealed a 5 mm raised erythematous area of the mucosa. Close inspection of this lesion showed a sentinel flap of mucosa overlying a slit which communicated with large vascular spaces in the mucosa and submucosa. These spaces led into vascular lacunae in the external muscle coat and serosa which drained into several thick walled vessels. Histological sections demonstrated that the walls of the mucosal vascular spaces were lined by smooth muscle broken up by collagen and elastic tissue. Furthermore, the walls of the draining vessels had features of 'arterialization' with areas of intimal thickening and elastic reduplication.

The patient made a satisfactory recovery and was alive and well at follow-up 2 months later.

Discussion

'Ectopic' varices are estimated to occur in approximately 1–3 per cent of patients with cirrhosis[1]. They occur predominantly in the digestive tract and at enterostomies, the most common site being at an ileostomy, in which case the liver

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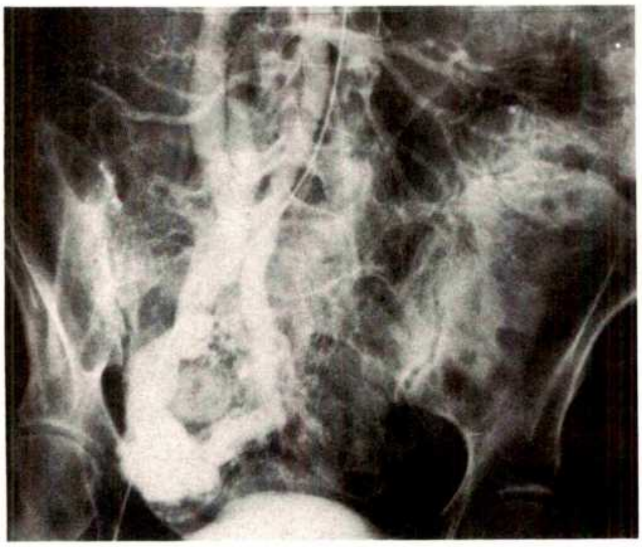

Figure 1 *Venous phase of selective superior mesenteric angiogram showing venous pooling in the pelvis and two large mesenteric veins*

disease may be secondary to ulcerative colitis. The first case of bleeding from varices in the small intestine was described in 1961[2]. Since then, few patients with this condition have been described and there is no evidence that the incidence of ectopic varices is increasing[1].

Patients with varices in the small intestine have usually undergone previous intra-abdominal surgery, commonly many years before they present with gastrointestinal bleeding[1]. It is therefore thought that adhesions provide the communication between the portal and systemic venous systems[3].

Unlike most cirrhotics with gastrointestinal haemorrhage, haematemesis is not a feature of bleeding from jejunal or ileal varices. The predominant symptom is the passage of dark red blood *per anum* which is usually profuse. Endoscopy may reveal oesophageal varices or peptic ulceration but characteristically there is no blood in the upper gastrointestinal tract, even on laboratory testing of nasogastric aspirate. Under these circumstances the diagnostic procedure of choice is angiography. Care must be taken in interpreting the films, especially as radiological embolization of a presumed arterial lesion may cause mesenteric ischaemia. The venous phase of a selective superior mesenteric angiogram is usually diagnostic and demonstrates large venous 'pools' and grossly dilated mesenteric veins[4].

Since bleeding from ileal varices is most often profuse and recurrent, surgery should be undertaken as soon as the diagnosis is made. Portal–systemic shunting has been described[1] but we consider this technique inappropriate (particularly in an elderly female). Intestinal resection is a simple procedure which not only avoids the risk of encephalopathy but removes the source of bleeding.

The pathological findings in the ileum where it had been adherent to the side wall of the pelvis were unusual. In this region there were multiple large intramural vascular lacunae which were predominantly venous in structure but also had histological characteristics of 'arterialization'. These features may have been the result of a high pressure portal–systemic shunt.

The outcome of bleeding from varices in the small intestine is unfavourable judging by the few survivors reported in the literature[1]. Indeed, many deaths go unreported or remain of unrecognized cause. Nevertheless, an appreciation of the mode of presentation of this unusual cause of gastrointestinal bleeding, allied with prompt and appropriate diagnosis and surgery, can produce a successful outcome even in poor risk patients with massive haemorrhage.

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Association between extent of colonic mucosal sialomucin change and subsequent local recurrence after curative excision of primary colorectal cancer

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Two interrelated studies were carried out to determine whether extent of sialomucin change adjacent to a primary colorectal carcinoma predicted local tumour invasiveness and risk of local recurrence. In the first, depth of tumour penetration was correlated with the length of the sialomucin band adjacent to 72 primary colorectal cancers. There was a significant ($P < 0{\cdot}05$) *increase in sialomucin band length adjacent to tumours invading adjacent structures compared with those which had not (Mann–Whitney* U *test), although there was no overall correlation between depth of penetration, Dukes' classification or degree of differentiation (Kruskal–Wallis test). A sialomucin band of* >3 *cm was associated with a 70 per cent probability of adjacent structure* (T_4) *invasion. These observations were then tested prospectively in a second study involving 256 patients to determine whether the presence of a* >3 *cm sialomucin band could predict local recurrence. Presence of a* >3 *cm sialomucin band was a significant* ($\chi^2 = 7{\cdot}12$, *d.f.* $= 1$, $P < 0{\cdot}001$) *and independent predictor of local but not distant recurrence. In addition both the interval to local recurrence and survival were significantly shorter if a* >3 *cm sialomucin band was present. However the accuracy of* >3 *cm sialomucin band as a predictive test for local recurrence was only 70 per cent. The extent of sialomucin adjacent to a primary colorectal cancer does provide a crude assessment of tumour invasiveness and risk of local recurrence.*

Keywords: Colorectal cancer, local recurrence, sialomucin

Local recurrence causes death in up to 50 per cent of patients after apparently curative excision of primary colorectal carcinomas[1]. This can be reduced by more radical surgery[2] and adjuvant radiotherapy[3], but both these approaches are associated with increased morbidity. There is a need for a simple preoperative test which identifies patients at higher risk of local recurrence in whom additional treatments are justified. Local recurrence depends on extent of primary tumour local spread[4]. Preoperative endoluminal ultrasound[5] and computed tomographic (CT) scanning[6] provide some indication of local spread before excision of a rectal carcinoma but for colonic carcinoma, identification of high risk patients depends on pathological assessment of the resected tumour[7].

Alteration of carbohydrate side chain structure to form sialomucin is found in colonic mucin adjacent to 90 per cent of colorectal carcinomas[8]. The increased prevalence of this change adjacent to invasive carcinoma compared with adenomas[9] and non-neoplastic disorders[10] suggests that change in colonic mucin is potentiated by factors that are associated with malignant behaviour. Since risk of local tumour recurrence increases with extent of primary tumour local invasion[4], the degree of adjacent colonic sialomucin change might reflect extent of local tumour infiltration and hence indicate risk of local recurrence after primary tumour excision.

We have assessed whether the amount of sialomucin change adjacent to primary colorectal carcinoma identifies patients who are at risk of local tumour recurrence. Two related studies were carried out. We first assessed whether there was an association between primary tumour invasion into adjacent structures and length of sialomucin band in adjacent mucosa. This 'pathological' study suggested that a sialomucin band of >3 cm adjacent to the primary tumour was associated with an increased probability of tumour invasion into adjacent structures. We then carried out a prospective study in which the length of the sialomucin band was assessed as a predictor of local tumour recurrence.

Patients and methods

Pathological study

Resected specimens obtained from patients undergoing excision of primary colorectal carcinoma were opened and fixed in 10 per cent formal saline solution. After fixation a 1 cm wide longitudinal strip of colon was excised so as to include the centre of the tumour and both resection margins. Blocks were taken in a longitudinal axis along the length of the specimen and processed in paraffin. Sections 4 μm thick were cut and stained with haematoxylin and eosin and the high iron diamine-alcian blue stain (HID-AB)[11]. A consultant pathologist (H.C.R.) classified tumours according to Dukes' classification[12], Broder's differentiation[13] and Union International Contra le Cancrum (UICC) T (tumour) depth of invasion[14] by histological examination of haematoxylin and eosin stained sections from both the longitudinal strips and lymph nodes. Only when there was histological evidence of invasion into adjacent organs were tumours staged as T_4

Mucin stains were examined by two independent assessors (P.M.D and N.A.H.) Three mucin patterns were identified with the HID-AB stain: (1) sulphomucin secretion staining brown, (2) mixed sulphomucin and sialomucin secretion staining brown and blue, (3) sialomucin pattern staining blue. The first two patterns were regarded as normal[7] Using a definition of abnormal which required an entire ×60

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microscopic field to contain exclusively sialomucin, agreement between assessors was reached about mucin staining patterns in all cases after discussion. The length of the sialomucin band extending proximally or distally from the tumour edge was assessed using a microscope with an eyepiece graticule.

Clinical study

Patients undergoing 'curative' resection of histologically confirmed primary adenocarcinoma of the colon or rectum in six participating centres (see Acknowledgements) were studied. Specimens were received unfixed and biopsies taken at 1 cm intervals from tumour to both resection margins. The carcinoma was then categorized into tumour stage (Dukes' classification) and differentiation (Broder's classification) as above at the hospital of operation. A consultant pathologist (H C R.) reviewed 100 specimens to ensure uniformity of classification between pathologists. HID-AB stained sections were examined by two independent assessors (P M D, N.A H) and classified according to criteria given above. Curative resection and local recurrence were defined as previously reported[15]. Evidence of tumour recurrence was obtained from biopsy, CT scan, barium contrast radiography, ultrasound or by clinical examination. Survival was measured from time of primary tumour resection until death. Cause of death was obtained from the death certificate or, where possible (15 cases), from autopsy.

Statistical methods

Comparison between length of sialomucin band and tumour stage, differentiation and invasion was by Kruskal–Wallis test and Mann–Whitney *U* test. Correlation between tumour size and amount of sialomucin was by Rank–Spearman coefficient (r). Clinical variables were stored and analysed on computer using the SPSS package[16]. Local recurrence and survival were analysed by multivariate analysis using the Cox regression model[17]. This gave an estimate of the relative strength of each variable as a predictor of either local recurrence or survival. Deaths from causes other than cancer were treated as censored observations at the time of death in the local recurrence model. All deaths were considered in the survival models. Prognostic variables for the events 'local recurrence' and 'survival' were chosen by formal stepwise regression using the program BMDP2L[18]. Prognostic variables could thereby be selected in steps until no further significant effect upon the events could be demonstrated. Each prognostic variable was analysed as a survival predictor by life table analysis[19].

Results

Pathological study

A total of 72 carcinomas (right to mid transverse colon, 13; mid transverse to sigmoid, 9, sigmoid, 27; rectum, 23) obtained from 71 patients studied. Sialomucin change was absent in 10 (14 per cent) specimens (R:L, 4·6, Dukes' A, 1; B, 4; C, 5. well differentiated, 2, moderately differentiated, 8). There was no significant difference in distribution, stage or differentiation of tumours not associated with sialomucin change compared with those which were. Tumours not associated with sialomucin change were excluded from further analysis. Details of classification, differentiation and invasion of the remaining cancers are shown in *Table 1*. Sialomucin band could not be measured proximal to the tumour in eight cases owing to the proximity of the tumour to the ileum and in three cases owing to the proximity of the tumour to the anal margin.

The mean(s.d.) length of sialomucin band extending away from the primary tumour (either proximally or distally) was 3·1(2·9) cm. There was no significant difference between mean proximal (2·9(2·5) cm) and distal (2·5(2·4) cm) sialomucin band length. There was no significant difference in sialomucin band length between cancers situated proximal (mean 4·0(4·6) cm) and those distal (3·0(2·2) cm) to the splenic flexure.

There was a significant difference ($P<0.05$) in length (*Table 1*) of sialomucin band between tumours which had penetrated adjacent structures (UICC T_4) and those which had not (T_{1-3}) (Mann–Whitney *U* test). There was no difference between groups using the Kruskal–Wallis test for either tumour depth of penetration, Dukes' classification or differentiation (*Table 1*). If a sialomucin band of either >3 or <3 cm was chosen to stratify tumours into high and low risk of T_4 depth of invasion then there was a 70 per cent chance of T_4 depth of invasion if the sialomucin band was >3 cm and a 66 per cent chance of $<T_4$ invasion if the band was $\leqslant$3 cm. In addition sialomucin extended to the bowel resection margin significantly ($\chi^2=5{\cdot}9$, d.f. = 1, $P<0.02$) more often with T_4 invasive tumours (6/10, 60 per cent) compared with T_3 (10/46, 22 per cent). There was a poor correlation between sialomucin band length and maximum tumour diameter ($r=0.37$).

Table 1 *Length of sialomucin band (cm) by Dukes' classification, differentiation and depth of invasion of the primary tumour*

Variable		*n*	Length of sialomucin (cm) Median	Interquartile range	*P**
Classification (Dukes')	A	6	1·68	1·0–3·8	n.s.
	B	32	2·27	0·9–4·6	
	C	24	2·27	1·4–4·0	
Differentiation (Broder's)	Well	11	3·2	1·8–6·0	n.s.
	Moderate	40	2·3	1·0–4·0	
	Poor	8	2·9	0·6–2·7	
Invasion depth (UICC)	T_1	1	1·0		n.s.
	T_2	5	1·7	1·0–3·8	
	T_3	46	2·3	1·0–4·0	
	T_4	10	4·1	1·8–8·3	

* Kruskal–Wallis test

Table 2 *Site of primary carcinomas and incidence of sialomucin change in 256 patients undergoing curative resection*

Site	Total	Sialomucin band >3 cm *n*	Percentage of tumours at that site
Caecum	44	7	16
Ascending colon	20	3	15
Hepatic flexure	7	1	14
Transverse colon	11	2	18
Splenic flexure	7	2	28
Descending colon	12	1	8
Sigmoid colon	83	34	41
Rectum	69	25	36
Multiple	3	0	0

Table 3 *Prevalence of >3 cm sialomucin band length by age, sex, Dukes' classification and Broder's classification*

	All patients	Sialomucin band >3 cm
Age (mean, years)	66·8	67·3
Sex (M:F)	0·9:1	0·8:1
Dukes' classification (numbers of patients)		
A	26	6
B	143	48
C	87	21
Broder's differentiation (numbers of patients)		
Well	39	11
Moderate	188	53
Poor	29	11

Clinical study

The study was conducted on 256 patients (M:F 0·9:1, mean age 66·6 years) undergoing curative excision of primary colorectal cancer who survived the first 30 postoperative days. Details of tumour site are given in *Table 2* and tumour stage and differentiation in *Table 3*. There was no significant

Table 4 *Association between prevalence of >3 cm sialomucin band length and recurrence*

		Prevalence of recurrence		
Sialomucin band length	Total patients	Local *n*	Distant *n*	Local and distant *n*
⩽3 cm	181	13 (7)	22 (12)	14 (8)
>3 cm	75	7 (9)	6 (8)	15 (20)
Total	256	20 (8)	28 (11)	29 (11)

Values in parentheses are percentages

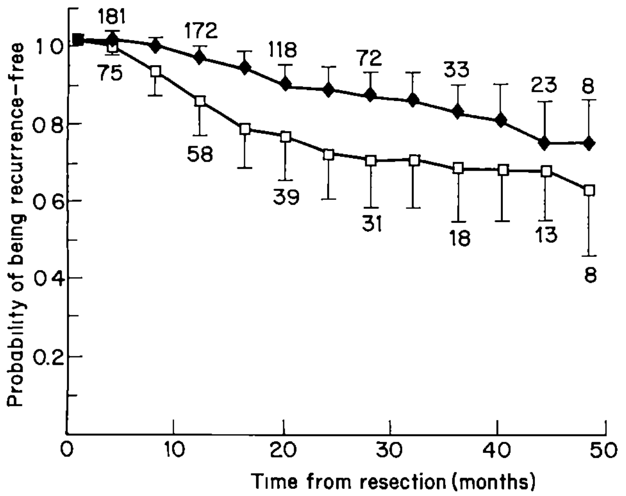

Figure 1 *Probability of remaining free from local recurrence with time from primary tumour resection*· ☐, *sialomucin* >3 *cm*, ◆, *sialomucin* ⩽3 *cm. Error bars indicate 95 per cent confidence intervals* (*Lee-Desu*=*9·3*, P<*0·002*)

difference in the prevalence of >3 cm sialomucin band by Dukes' classification, differentiation, age or sex of the patient. During a mean(s.d.) follow-up of 25·9(13·8) months, recurrence was detected in 77 patients (*Table 4*). Significantly more patients in the >3 cm sialomucin band group developed evidence of local recurrence compared with patients with ⩽3 cm band. This was confirmed by biopsy (40 patients), ultrasound (19 patients), pelvic CT scan (12 patients), clinical examination (six patients) and confirmed at autopsy in eight patients. Mean time to diagnosis of local recurrence was 11·8(2·3) months in the sialomucin positive group and 12·6(2·7) months in the sialomucin negative group. Univariate analysis suggested that interval to diagnosis of local recurrence was significantly shorter in patients with a >3 cm sialomucin band compared with those in whom this was absent (*Figure 1*).

Evidence of local recurrence with or without distant metastasis (*Table 4*) occurred significantly ($\chi^2=7·12$, d.f.=1, $P<0·001$) more frequently where a sialomucin band of >3 cm was present (22/75 patients, 29·3 per cent) than where it was absent (27/181 patients, 14·9 per cent). Cox model analysis of predictors of local recurrence demonstrated that the presence of sialomucin change >3 cm from the primary tumour was a significant ($P<0·001$) and independent predictor of local recurrence coming before Dukes' stage and differentiation in order of importance (*Table 5*). A similar Cox model analysis identifying predictors of survival (*Table 6*) selected sialomucin change as a significant survival predictor after Dukes' classification but before differentiation and hospital of operation. A Cox analysis of predictors for distant metastasis selected Dukes' classification as the only important independent predictor (global $\chi^2=22·89$, d.f.=1, $P<0·001$). Univariate analysis (*Figure 2*) demonstrated that a sialomucin band of >3 cm was associated with shorter survival than if this was absent.

Discussion

Factors associated with increased local recurrence of colorectal cancer are: wide local spread of primary tumour[4,20], inaccessible location[21], and inadequate surgical technique[2]. Any attempt to predict local recurrence purely on the basis of tumour characteristics will be limited by the interrelation of these variables. Thus a localized Dukes' B carcinoma situated in the lower third of the male rectum which is inadequately excised has a high risk of local recurrence, whereas a locally invasive Dukes' B carcinoma of the sigmoid colon involving bladder and uterus which is completely excised does not[7]. Incomplete excision of an inaccessible but minimally invasive carcinoma will tend to reduce the sensitivity as a predictor of local recurrence of any test assessing tumour behaviour, whereas complete radical excision of a highly invasive tumour will reduce specificity.

Nevertheless, it would be useful to predict before operation those tumours with greatest propensity for local recurrence since, given a particular surgeon and tumour site, risk of local recurrence increases with extent of local tumour invasion[4]. Such

Table 5 *Selection of Cox regression model for 'local recurrence' related parameters. Deaths other than cancer have been censored*

	χ^2 to enter into model			
Parameters	Step 0	Step 1	Step 2	Step 3
Operation*	0·73	0·02	0·01	0·00
Dukes' stage	10·69	11·70	$\underline{11·70}$	$\underline{9·13}$
Differentiation	9·79	10·50	7·93	$\underline{7·93}$
Margin <5 cm	7·01	5·77	4·97	7·29
Size >5 cm	0·91	1·29	0·66	0·70
Sialomucin >3 cm	11·66	$\underline{11·66}$	$\underline{12·67}$	$\underline{12·64}$
Sex	0·47	0·97	0·53	0·50
Depth†	4·41	3·30	3·22	3·01
Hospital 1	0·30	0·14	0·37	0·10
Hospital 2	1·42	2·01	2·69	2·04
Hospital 3	2·62	2·20	2·05	2·28
Hospital 4	0·22	0·00	0·08	0·08
Hospital 5	3·35	2·40	2·96	3·16
Hospital 6	0·84	0·10	0·00	0·13
Global χ^2		12·89 d.f.=1	25·76 d.f.=2	37·5 d.f.=3
P value (improvement)		<0·001	<0·001	<0·001

Underline denotes parameter has been entered into the model, χ^2 denoted by underline denotes value to remove from model. * Right *versus* left, † T_{1-3} *versus* T_4

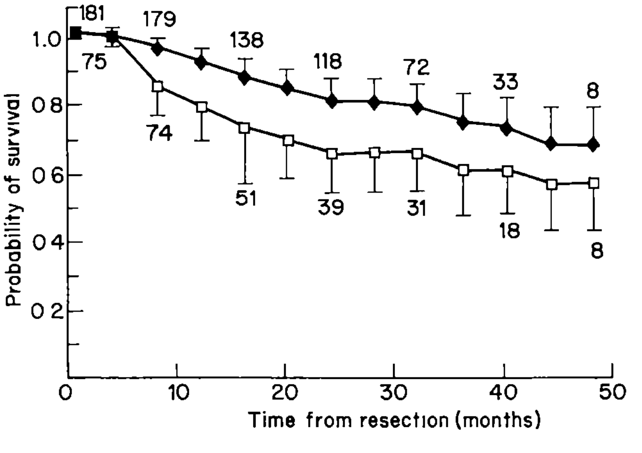

Figure 2 *Probability of survival with time after primary tumour resection* ☐, *sialomucin* >3 *cm*, ◆, *sialomucin* <3 *cm. Error bars indicate 95 per cent confidence intervals* (*Lee-Desu*=*8·7*, P<*0·003*)

Table 6 *Selection of Cox regression model for 'survival' related parameters Deaths due to other causes have been included*

Parameters	χ^2 to enter into model				
	Step 0	Step 1	Step 2	Step 3	Step 4
Operation*	0·21	0·13	0·15	0·25	0·54
Dukes' stage	25·26	$\underline{23{\cdot}48}$	$\underline{25{\cdot}31}$	$\underline{20{\cdot}98}$	$\underline{18{\cdot}32}$
Differentiation	19·00	14·68	14·30	$\underline{13{\cdot}47}$	$\underline{15{\cdot}93}$
Margin <5 cm	1·55	1·09	0·56	0·05	0·18
Size >5 cm	3·10	1·90	2·29	2·34	1·66
Sialomucin >3 cm	15·03	17·03	$\underline{16{\cdot}19}$	$\underline{15{\cdot}95}$	$\underline{18{\cdot}04}$
Sex	0·78	0·97	0·85	0·79	0·44
Depth†	0·00	0·01	0·21	0·28	0·01
Hospital 1	1·51	1·08	1·06	1·85	1·05
Hospital 2	1·73	3·44	3·81	2·69	3·51
Hospital 3	0·85	0·92	0·56	0·75	0·02
Hospital 4	2·39	1·23	2·84	5·39	$\underline{5{\cdot}21}$
Hospital 5	0·14	0·09	0·15	0·14	0·13
Hospital 6	0·49	0·27	0·13	0·00	0·07
Global χ^2		25·25 d.f.=1	41·95 d.f.=2	58·99 d.f.=3	63·93 d.f.=4
P value (improvement)		<0·000	<0·000	<0·001	<0·032

Underline denotes parameter has been entered in the model; χ^2 denoted by underline denotes value to remove from model. * Right *versus* left, † T_{1-3} *versus* T_4

information would help to determine whether preoperative adjuvant treatment[22] or referral to a specialist colorectal surgeon[23] was desirable. In this study, to overcome the misleading conclusion that might result from using local recurrence as the sole endpoint, we have also examined the ability of sialomucin change to predict whether the primary tumour has spread to adjacent structures.

Little is known of the factors that stimulate colonic sialomucin change. It can be produced by mucosal trauma or inflammation[10], but the prevalence increases adjacent to dysplasia[24] and neoplasia[8], and increases still further with progression to malignancy in the adenoma–carcinoma sequence[25,26]. Since sialomucin change usually arises adjacent to diseased colonic mucosa, it appears to be stimulated by agents released following cell damage and proliferation in nearby diseased epithelium. The aim in this study was to determine whether factors stimulating colonic sialomucin change were also associated with increased tumour invasiveness.

Tumour products predisposing to invasiveness include: collagenases[27], cathepsin B[28], plasminogen activator[29], and angiogenic factors[30]. The association[15], also found in the present study, between local tumour recurrence and lymph node metastasis supports animal xenograft observations[31] that local invasiveness correlates with blood- and lymphatic-borne spread since local vascular invasion is a prerequisite for metastasis.

In the present study, there was an association between extent of sialomucin change and tumour penetration through the bowel wall into adjacent structures There were fewer cases of T_1 and T_2 depth of invasion which reduced the power of analysis. However sialomucin change did not appear sufficiently sensitive to provide information about lesser degrees of bowel wall invasion. The presence of a >3 cm sialomucin band correlated with local but not distant recurrence. Thus sialomucin change reflected factors influencing local invasiveness but not tumour metastatic potential. The association between sialomucin change and survival can be attributed to the high mortality rate of local recurrence[1].

The low sensitivity of sialomucin as a predictor of depth of invasion was also found for local recurrence in the clinical study. If sialomucin change on biopsy at >3 cm from the tumour was used to predict local recurrence, then predictive accuracy was only 70 per cent (sensitivity 44 per cent, specificity 75 per cent). Nevertheless the incidence of local recurrence among patients in whom a >3 cm sialomucin band was present was double that of patients in whom it was absent, and occurred significantly earlier after primary resection if a >3 cm sialomucin band was found. There are few biological predictors of local tumour behaviour and a mucosal biopsy taken 3 cm from the tumour edge which shows sialomucin provides unique preoperative clinical information. Prediction of tumour natural history requires staging methods based on factors directly associated with tumour behaviour. The prerequisite to this and, therefore, to tumour staging, is an improved understanding of factors responsible for tumour invasiveness.

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Case report

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Pouchitis following colectomy and ileal reservoir construction for familial adenomatous polyposis

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Acute reservoir ileitis (pouchitis) has been reported in 7–43 per cent of patients following colectomy and ileal reservoir formation[1] and is characterized by episodic diarrhoea in the presence of acute inflammatory changes in the pouch mucosa. As acute reservoir ileitis has only been described in patients with a previous diagnosis of ulcerative colitis[2], the aetiology of pouchitis may be disease-related. However, the efficacy of metronidazole in the treatment of pouchitis suggests that faecal organisms may also have a role in the pathogenesis of pouchitis[2].

We report the first fully documented case of pouchitis in a patient following ileal reservoir construction for familiar adenomatous polyposis.

Case report

A 23-year-old Caucasian male had an elective restorative proctocolectomy performed for familial adenomatous polyposis as a single-stage procedure using a double loop ileal J pouch. Mucosal proctectomy was completed to the dentate line before a sutured ileoanal anastomosis

Following an uncomplicated 10-month postoperative course the patient presented with sudden onset of malaise, increased frequency of defaecation by day (eight times) and night (two times), urgency and nocturnal leakage of faecal fluid *per anum* sufficient to require the use of two pads Examination revealed mild diffuse abdominal tenderness with no evidence of an anal stricture

Sigmoidoscopy of the pouch revealed patchy mucosal erythema with spontaneous bleeding and multiple pouch biopsies demonstrated mucosal ulceration, villous atrophy, a heavy neutrophil infiltrate and crypt abscesses. Faecal bacterial culture failed to detect a specific enteropathogen or increased numbers of aerobic or anaerobic bacteria An indium-labelled granulocyte scan showed increased activity in the region of the pouch which was confirmed by increased radioactivity in a concurrent 4-day faecal collection (4 per cent of total injected radioactive dose, normal <2 per cent[3]).

Following 1 month's treatment with metronidazole symptoms had improved with complete resolution of urgency and soiling The endoscopic and histological appearances of the pouch mucosa were now indistinguishable from the appearances in healthy ileal reservoirs. A repeat indium-labelled granulocyte scan showed no abnormality and a repeat 4-day faecal collection did not show increased indium granulocyte excretion.

Discussion

This case demonstrates that pouchitis can occur in the absence of ulcerative colitis, anal stenosis, bacterial overgrowth or a specific enteropathogen. We have used sigmoidoscopic, histological and microbiological criteria for diagnosing pouchitis[2] to exclude clinical syndromes causing diarrhoea that may mimic the features of acute reservoir ileitis such as overflow incontinence due to an anal stricture, Crohn's disease[2] and jejunal bacterial overgrowth[4]. Acute inflammation in the pouch was confirmed objectively by a positive radiolabelled granulocyte scan and by increased faecal excretion of labelled granulocytes.

Response to metronidazole in the absence of increased pouch anaerobic bacterial counts is accepted as the usual sequence of events in pouchitis[5] These findings, however, do not exclude a possible role for bacterial metabolites in the aetiology of acute reservoir ileitis[5].

This report illustrates a case where pouchitis has occurred in the absence of ulcerative colitis, casting doubt on previous reports that have suggested a common aetiology[2,5].

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Direct measurement of collagenase in colonic anastomosis

Collagenase has been implicated in colonic anastomotic dehiscence but the enzyme has not previously been specifically measured in colonic healing. A 72 h tissue culture method for colonic tissue and a radiochemical assay for collagenase were adapted to measure the enzyme in healing rabbit colon, with specificity of the assay confirmed by sodium dodecylsulphate polyacrylamide gel electrophoresis. Normal and postoperative colon secreted collagenase, predominantly in a latent form, in the first 24 h of culture. Total activity reached a plateau after 48 and 72 h in culture, when 50–70 per cent of the enzyme was in an active form. At these times in culture, activity was significantly higher than after 24 h ($P<0{\cdot}001$)*. One day after anastomosis the total amount of collagenase secreted in culture was higher than normal but the increase did not achieve significance. Three days after anastomosis the colon secreted more collagenase than explants from 1 day postoperative tissue* ($P<0{\cdot}002$)*. The proportion of active enzyme in the first 24 h in culture was also increased. Since active collagenase can be measured in culture medium from both normal and postoperative colon, the tissue may be secreting plasminogen activator which allows plasmin to activate the enzyme. The increase in collagenase after operation coincided with a decrease in collagen concentration in the colon wall, measured by hydroxyproline. This supports previous suggestions that collagenase contributes to anastomotic dehiscence. However, the findings must be interpreted with caution as the variance of the results was shown to be predominantly due to time in culture, suggesting this could be a bigger influence than the operation itself. In addition, our previously reported immunohistochemical study of this system indicated that collagenase only occurred in a localized region, restricted to the everted portion of the anastomosis, with the activity being tightly controlled by its inhibitor, tissue inhibitor of metalloproteinases.*

Keywords: Colorectal surgery, collagen, collagenase

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Dehiscence of a large bowel anastomosis is a major complication of colonic surgery, prolonging hospital stay and increasing mortality rate from 7 to 22 per cent[1] Left-sided anastomoses break down more frequently than those on the right[2] and, while many factors including obstruction, ischaemia and infection are known to interfere with colonic healing[3], the mechanism of this impairment is poorly understood.

Collagen is a major structural component of the colon wall and many studies have shown significant reductions in the concentration of this protein at the site of anastomosis in the early postoperative period[4–6]. In a study of collagenolytic activity in the rabbit, Hawley and colleagues found greater collagenolysis in normal left colon than in the rest of the gastrointestinal tract and activity increased two and a half times around an anastomosis on the third postoperative day[7]. These reports suggested that excessive collagen degradation contributed significantly to the process of anastomotic breakdown and the enzyme collagenase was therefore implicated as the key factor in colonic dehiscence This specific enzyme however, has not previously been measured directly in colonic tissue following anastomosis.

Degradation of mature extracellular collagen is initiated by the specific metalloproteinase, collagenase, which is synthesized as required and secreted in a latent form[8]. The enzyme binds closely to its collagen substrate and active collagenase is rapidly inhibited by formation of a complex with tissue inhibitor of metalloproteinases (TIMP). In a previous qualitative study using immunohistochemistry[9], we demonstrated the presence of collagenase confined closely to the region of the anastomotic suture line. We have adapted a tissue culture system and a specific radiochemical assay in order to measure collagenase in the colon and thus quantify the enzyme at the site of an anastomosis.

Materials and methods

Preparation of tissue

Colon segments, 2 cm long, were resected from a standard site in the distal colon of ten female New Zealand White rabbits (weight 1 5–2·5 kg), under pentobarbitone anaesthesia (45 mg/kg intravenously) and single layer everted anastomoses were formed with interrupted 6/0 silk sutures. The resected segments were processed immediately and served as controls for the postoperative tissue in each animal Five animals each time were killed by pentobarbitone overdose, 1 and 3 days after operation and 5 cm segments of colon with the anastomosis at the centre were removed. Colon segments were opened lengthwise to remove the contents and washed in five changes of Hank's balanced salts solution containing 100 units/ml penicillin, 100 μg/ml streptomycin and 2 5 μg/ml amphotericin B, with the first three washes containing ten times these concentrations of antibiotics. The anastomotic segment was divided to give four strips of tissue, two from immediately proximal and distal to the stitch line (P_0 and D_0) and two from 2 cm further in each direction (P_2 and D_2) Four full-thickness explants, each weighing approximately 40 mg, were cut from the resected control segments and from each postoperative strip of colon for tissue culture The remaining

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tissue from each strip was homogenized in water and lyophilyzed for hydroxyproline assay.

Explants for collagenase activity were placed individually on stainless steel grids in 3·5 cm diameter tissue culture wells. The tissue was cultured at 37°C for 72 h in 4 ml Dulbecco's modification of Eagle's medium containing 20 mmol HEPES (Flow Laboratories, Irvine, UK), 1 per cent (v/v) acid-treated fetal calf serum (Flow Laboratories), 2 mmol L-glutamine, 0·5 mg/ml sodium bicarbonate and antibiotics as in the Hank's solution. The medium was replaced every 24 h for 72 h and used medium was stored in 0·2 per cent sodium azide at −20°C until assay for collagenase activity.

Hydroxyproline assay

Freeze-dried tissue was hydrolysed in 2M HCl for assay of hydroxyproline content by a modification of the method of Woessner[10]. After neutralization and dilution, chloramine-T initiated oxidation of the hydroxyproline to pyrrole. Perchloric acid destroyed the chloramine-T and 4-dimethylaminobenzaldehyde was then added to form a chromagen which reflected the hydroxyproline content and could be measured spectrophotometrically. The mean value from five aliquots of tissue homogenate gave the result for each segment of colon, expressed as μg hydroxyproline per mg dry tissue.

Assay for collagenase activity

Samples of culture medium were assayed for collagenase activity by the method of Cawston and Barrett[11]. Aliquots of medium were incubated with 100 μg ^{14}C-collagen (acid-soluble collagen, Sigma UK Ltd, Poole, UK labelled with ^{14}C-acetic anhydride, Amersham International, Amersham, UK) in 100 mM Tris/HCl, pH 7·6, containing 15 mmol $CaCl_2$ and 3 mmol phenylmethylsulphonyl fluoride (PMSF), for 15 h at 35°C. The modifications of Terato *et al.*[12] were used for termination of the reaction and separation of any remaining intact collagen from digested fragments. The reaction was stopped by the addition of 5 mmol 1,10-phenanthroline (20 μl of 80 mM solution in 50 per cent dioxane added to 0·3 ml reaction mixture) and after incubation for a further hour to allow undigested collagen to form fibrils, 400 μl dioxane/methanol (4·1) was added to extract the peptide fragments. Undigested collagen was separated by centrifugation for 5 min at 11 000 *g* in a Hawksley (Lancing, UK) Microhaematocrit centrifuge. A volume of 400 μl of supernatant was mixed with 3 ml liquid scintillant (Packard ESS 299, Canberra Packard, Pangbourne, UK) and counted on a Packard Tri-carb 2000CA liquid scintillation counter to measure collagen degradation.

Non-specific collagen breakdown was assessed by control tubes containing collagen and buffer only or 10 μg trypsin, while total lysis was determined by the addition of 100 μg bacterial collagenase. Medium samples were assayed in triplicate at four different dilutions to measure their active collagenase content. To measure total activity, duplicate sets were treated with 0·67 mM 4-aminophenylmercuric acetate (APMA) to activate any latent enzyme.

The active and total collagenase activity of medium from each explant was measured for each 24 h in culture and the mean values from four explants gave the results for each individual segment of colon. Activity was expressed in units/mg wet weight of tissue, where one unit of collagenase degrades 1 μg of collagen per minute at 35°C.

The specificity of the assay for collagenase was investigated by incubating activated samples with collagen at 25°C. Sodium dodecylsulphate polyacrylamide gel electrophoresis (SDS-PAGE) was carried out to examine the reaction products[13] and demonstrated that the reaction products were 3/4 and 1/4 fragments of collagen, confirming the specificity of the assay for collagenase[11,14].

The data are expressed as means and standard error of the mean for groups of five animals. To analyse the results of collagenase activity, the data were pooled into two groups, total and active and analysed by one or two way analysis of variance using the computer package, Minitab (Minitab Inc., State College, Pennsylvania, USA). Each of the factors investigated, time in culture, the postoperative day on which the animal was killed and the site from which the explant was taken, were separately examined against the data as a whole to determine which contributed most to the variance of the results.

Results

Hydroxyproline concentrations

The results for hydroxyproline concentration in normal and postoperative colon are detailed in *Table 1*. There were no changes in hydroxyproline concentration in any of the segments on the first postoperative day. On the third day, hydroxyproline remained normal distally but decreased proximally, both at the stitch line (P_0) and 2 cm distant (P_2), although statistical significance was not reached.

Table 1 *Mean(s.e.m.) values from five rabbits of hydroxyproline μg/mg dry weight on the first and third postoperative days*

Tissue	Mean(s.e.m.) hydroxyproline μg/mg dry weight First postoperative day	Third postoperative day
Control	11·1(1·3)	11·5(0·9)
P_2	14·5(2·4)	8·5(0·7)
P_0	10·8(2·3)	7·6(0·7)
D_0	11·3(2·5)	10·8(0·9)
D_2	9·6(1·5)	11·9(1·3)

P_0, P_2, proximal to stitch line, D_0, D_2, distal to stitch line

Table 2 *Mean(s.e.m.) values from five rabbits in enzyme activity units × 10^{-3}/mg wet weight on the first and third postoperative days following 24, 48 and 72 h of culture*

Hours of culture and tissues	First postoperative day		Third postoperative day	
	Total	Active	Total	Active
24 h				
Control	33·9(6·2)	1·2(0·9)	51·7(18·6)	8·9(6·7)
P_2	32·7(10·2)	3·0(2·1)	96·8(30·0)	31·4(24·7)
P_0	23·6(9·9)	0·3(0·3)	77·5(21·8)	10·7(5·9)
D_0	34·4(5·7)	4·9(2·8)	101·9(34·5)	41·0(16·6)
D_2	54·7(16·5)	27·8(15·4)	85·3(37·7)	48·2(29·1)
48 h				
Control	356·6(25·7)	222·8(10·3)	368·5(58·5)	223·2(42·1)
P_2	421·9(55·7)	261·0(34·6)	691·2(138·5)	489·1(149·5)
P_0	391·3(63·2)	189·1(6·8)	612·3(102·6)	435·4(95·8)
D_0	363·1(55·3)	264·0(28·4)	672·1(123·2)	458·1(122·3)
D_2	398·2(48·0)	269·1(29·2)	488·6(100·0)	331·9(76·1)
72 h				
Control	378·3(62·9)	235·7(32·3)	331·8(40·2)	205·8(35·5)
P_2	528·3(97·5)	283·0(26·3)	573·1(22·5)	417·5(33·4)
P_0	351·8(78·1)	172·2(29·5)	512·7(52·9)	345·2(47·7)
D_0	422·3(47·6)	249·1(27·7)	621·2(63·0)	420·6(27·8)
D_2	468·1(113·7)	249·6(36·4)	611·5(67·1)	379·4(45·3)

P_0, P_2, proximal to stitch line, D_0, D_2, distal to stitch line

Collagenase activity

Enzyme activity was measured in all samples of culture medium, both from control and postoperative colon and the results are shown in *Table 2*. The activity measured after 24 h of culture was considerably less for all explants than that after 48 and 72 h in culture (*Figure 1a*). Collagenase secreted after 24 h in culture was predominantly in a latent form with the exception of the D_2 segment when 50 per cent of the activity was secreted in an active form at both 1 and 3 days after operation. In contrast, the greater proportion of collagenase secreted after longer periods in culture was in an active form, 50–60 per cent after 48 h and 70 per cent after 72 h. Collagenase activity was higher from animals killed on the third postoperative day than on the first (*Figure 1b*), although the pattern of secretion of collagenase was the same in all explants.

Analysis of variance showed that the site from which the tissue had been removed had no influence on the variance of the results, i.e. the control segment, P_0, P_2, D_0 and D_2 from any one period all secreted the same amount of collagenase (*Figure 1c*). Although the control segment secreted less collagenase than tissue from rabbits on which an anastomosis had been performed this was not a significant difference.

Significantly more collagenase activity was secreted by explants removed from rabbits 3 days after anastomosis compared with those from 1 day postoperative animals ($P < 0·002$) (*Figure 1b*).

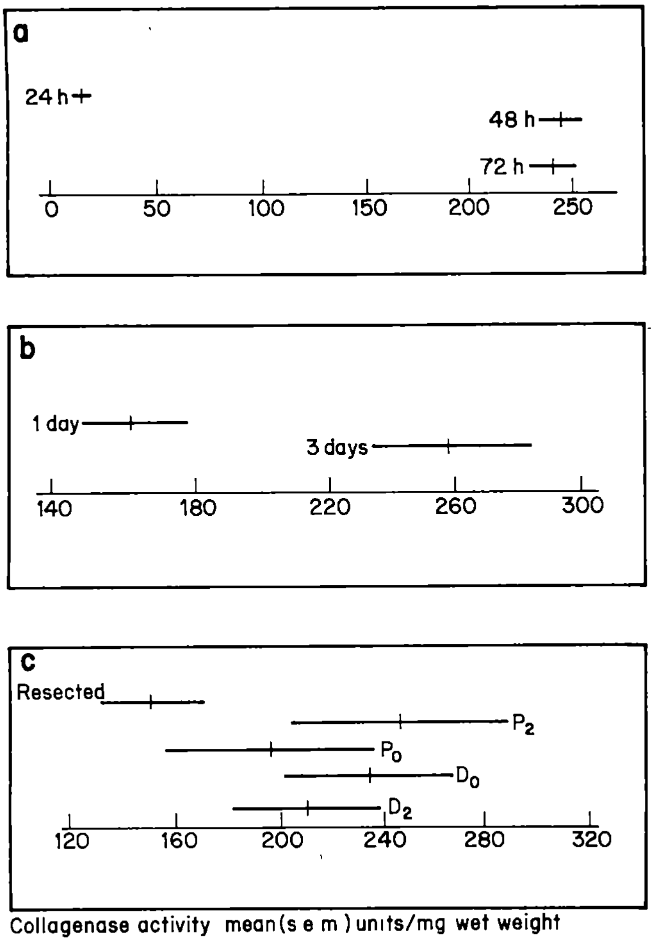

Figure 1 *Diagrammatic representation of analysis of variance (Minitab)* **a** *Time in culture, activity is higher after 48 and 72 h of culture than after 24 h,* $P<0\cdot001$. **b** *Activity on third postoperative day is significantly higher than activity on first day,* $P<0\cdot002$. **c** *There is no difference in activity with site from which the explant has been removed, although the resected segment has lower activity this is not significantly different*

Investigating the effect of time in culture on the spread of results demonstrated that medium collected from the first 24 h of culture secreted significantly less collagenase activity than medium collected after 48 or 72 h culture ($P<0\cdot001$) (*Figure 1a*).

A two-way analysis of variance showed that the spread of the pooled results was due almost entirely to time in culture and postoperative day ($P<0\cdot5$), with the two being independent of each other. Of these, time in culture had the most significant effect on the variance of the results.

Discussion

Our measurements of hydroxyproline are consistent with the findings of others[4–6] in that we observed a decrease in collagen concentration after operation in the colon wall proximal to an anastomosis However, this decrease did not achieve statistical significance. No explanation for this selective discrepancy has been found. Some degradation of collagen must occur during healing to remove damaged tissue at the site of transection and to allow restoration of continuity of the wall Thus, an increase in collagenase activity might be expected after anastomosis as this enzyme is necessary for the first step in extracellular collagen breakdown[8]. Measurements of collagenolytic activity by Hawley *et al*[7] suggest that, in colon, a greater increase in collagenase activity takes place than might be predicted for the remodelling required and that this is a major factor in the dehiscence of colonic anastomoses.

The major criticism of Hawley's work is that the lysis of collagen gels used for measurement may be due to the action of non-specific proteolytic enzymes, but considerable difficulties are encountered when establishing a specific assay for collagenase. The enzyme is tightly bound to its collagen substrate, the latent form requires activation and the reaction products must be separated and examined to ensure specificity of the assay for collagenase[7]. Neither we nor others[14] have been able to detect collagenase activity in uncultured colonic tissue and therefore a tissue culture system was developed for this study. The radiochemical assay described by Cawston and Barrett[11] was adapted for measurements of colonic tissue and SDS-PAGE confirmed the specificity of the activity being measured.

The present study demonstrates that normal rabbit colon secretes a specific collagenase into culture medium. This is in agreement with the findings of Oyamada *et al.*[14] and, although our measurements cannot be directly compared because of major differences in methodology, the pattern of enzyme secretion against time in culture confirms Oyamada's results. This is similar to the findings in pig synovium[15], bovine dental pulp[16], human gingiva[17] and rheumatoid synovial cells[18]. The lag phase found in the first 24 h in all these tissues is attributed to the fact that collagenase is synthesized on demand, with the stimulus for synthesis being provided by the culture conditions.

The proportions of active and latent collagenase secreted in culture vary in different tissues. Synovial cells[15], dental pulp[16] and normal gingiva[17] secrete almost entirely latent enzyme, even after several days in culture, while inflamed gingiva[17] and skin extracts[19] produce greater amounts of the active form. In contrast, colon in this study secreted some active enzyme from the first 24 h in culture and, in later samples, two-thirds of the collagenase was in the active form, similar to the proportion found by Oyamada *et al.*[14]. Both investigations therefore suggest that colonic tissue itself produces a factor which can activate latent collagenase, directly or indirectly, as has been demonstrated in skin[19]. Trypsin, plasmin and organomercurials are known and used as collagenase activators 'in vitro' and there is evidence that plasmin may be the 'in vivo' activator in some tissues[18]. Collagenase secreted by cultured fibroblasts was only partially activated by plasmin, full activation being achieved with stromelysin, although stromelysin alone would not activate collagenase[20]. The addition of serum to our culture medium provides a source of plasminogen which can be converted to plasmin if the tissue secretes plasminogen activator, as has been shown for both human[21] and rat colon[22]. The presence of serum has been shown to be essential for the colchicine-induced collagen breakdown of synovium[23].

As might be expected from the fall in hydroxyproline, colonic collagenase activity increased after operation, particularly in those animals killed on the third postoperative day. The trauma of resection and anastomosis should provide a stimulus to collagenase secretion but the effects of culture may influence the measurements as much as the enzyme activity in the tissue at the time of removal from the animal. This is suggested by the highly significant increase in activity after 24 h in culture. Secretion of enzyme by explants from postoperative colon still showed a lag phase in the first 24 h of culture, although a greater proportion of the collagenase tended to be already active, particularly on the distal side of the stitch line; if high collagenase activity was responsible for left-sided anastomotic breakdown, an increased level of activity should be apparent immediately the tissue was placed in culture. The persistence of the lag phase suggests that the stimulus of placing the tissue in culture is outweighing the effects of the operation and this is supported by the analysis of the results which showed that their variance was largely due to time in culture. However, Heath *et al.*[17] reported increased secretion of collagenase from explants of inflamed gingiva compared to normal, with active enzyme released only by the diseased tissue, and Barnes and Douglas[24] found different patterns of secretion in vulval explants from patients with different pathological conditions.

Both reports indicate that the measurement of collagenase in culture medium may at least partially reflect the state of the original tissue.

The total amount of enzyme secreted by the colon after 72 h culture increased after anastomosis, particularly on the third postoperative day. This increase in collagenase secretion coincided with a decrease in hydroxyproline concentration on the third day. Hendricks *et al.*[25] reported that the collagen level in colon reaches a trough 2 days after anastomosis and that the decrease is significant even at 1 day. Although this would precede the changes in collagenase, our own hydroxyproline levels are not significantly reduced at 1 day and must be taken as a more valid comparison, since they are measured on the same strips of tissue as provided the explants for collagenase assay.

These results support Hawley's original suggestion that increased collagenase secretion is responsible for the fall in collagen in the postoperative colon wall[7] However, caution is required in drawing this conclusion since it has been suggested that the measurement of active collagenase in culture medium represents only the overspill of enzyme which is not bound either to collagen or to TIMP[15]. Indeed, by immunolocalization methods we have been unable to demonstrate any abundance of collagenase at the site of an anastomosis[9]. Nevertheless, the present results could indicate a net increase in collagenase activity, due either to an increase in synthesis or to a decrease in inhibition. Current evidence suggests that the cytokines, particularly interleukin-1, are major stimulators of collagenase production 'in vivo'[8] and these are probably released by inflammatory cells gathering at the site of operation. In view of the encouraging reports of improved healing with the administration of proteinase inhibitors in animals[26,27] further application of this specific assay for collagenase would help to define the precise therapeutic possibilities in the prevention of colonic anastomotic dehiscence. However, with our present understanding of the mechanisms of collagenase activity, it is essential that future studies also pay attention to the role of TIMP in the healing mechanism.

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Intraluminal pressure adjacent to left colonic anastomoses

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A cumulative total of 89 h of pressure data was acquired from both sides of a left colonic anastomosis in 15 patients over a median period of 7 postoperative study days. Patients had a colonic ileus lasting 3–10 days and during this proximal and distal inactivity the intraluminal pressure remained within 6 mmHg of atmospheric pressure. After recovery of activity, pressures proximal to the anastomosis in excess of 10 mmHg occurred during less than 1 per cent of the recording time. Distal peak pressures were significantly elevated with respect to the proximal site ($P<0.001$)*. Two-thirds of the distal pressures recorded were between 10 and 20 mmHg and 98 per cent were less than 50 mmHg; the peak distal pressure was 90 mmHg. Four patients had distal repetitive tonic contractions creating a pressure difference across the anastomosis with a mean of 20 mmHg and a peak of 45 mmHg. Each contraction persisted for 15–20 min. Intraluminal pressures are unlikely to play a role in anastomotic dehiscence.*

Keywords: Anastomosis, pressure, manometry

The aetiology of colonic anastomotic dehiscence is multifactorial. In a retrospective study Irvin and Goligher[1] found that dehiscence was most common after anterior resection when compared with other elective colonic resections. Goligher *et al*[2] found that dehiscence (identified digitally, sigmoidoscopically or by barium enema) had occurred in 18 of 26 cases of low anterior resection (69 per cent) and in 19 of 47 cases (40 per cent) of high anterior resection Factors predisposing to dehiscence were increasing age, low serum proteins, extensive malignancy and poor bowel preparation. A low perianastomotic tissue oxygen tension has been shown to be related to an increased risk of anastomotic dehiscence[3,4].

An elevation in the intraluminal pressure during the postoperative period might predispose to anastomotic dehiscence Intraluminal pressures in the early postoperative period have not previously been studied. We therefore recorded the postoperative intracolonic pressure on either side of a left colonic anastomosis to determine basal pressures, and to see if there was a pressure gradient across the anastomosis and if high pressures occurred during colonic contractions.

Patients and methods

Fine-bore open-ended saline perfused tubes were chosen as the most suitable method of pressure transmission This technique ensured precise fixation at a chosen site, was independent of a limited battery life and recorded the true intraluminal pressure.

Each one of four tubes was connected via a perfusion system to a Gould P50 transducer (Spectromed Ltd., Coventry, UK), an Electromed four-channel amplifier (Ormed Ltd , Welwyn Garden City, Hertfordshire, UK) and chart recorder The transducer output was stored in digital form using the on-board analogue-digital converter of a BBC B+ microcomputer (Acorn Computers Ltd., Cambridge, UK).

The equipment was assembled on a trolley enabling the recordings to be done at the bedside, minimizing patient disturbance.

Twelve control patients were studied for 1 h per day for a total of 38 study days (cumulative total of 47 h of data) Ten were undergoing cholecystectomy and two had inguinal herniorrhaphies under general anaesthesia This group was studied to ascertain if it was possible to record the same pressure at the same site on four independent channels and to provide an indication of the range of colonic activity. These control patients had a mechanical bowel preparation the day before operation and following induction of anaesthesia had the tip of the tube assembly positioned in the sigmoid colon via a rigid sigmoidoscope The assembly consisted of four fine-bore tubes glued together to form a square in cross-section The tubes were sealed at one end with a single side hole drilled in each tube at right angles to each other in the same plane. Data were acquired for a minimum of 1 h on each postoperative day until the first bowel motion when the tubes fell out (mean of 3 days). One hour was chosen as this was the longest time patients could tolerate remaining immobile Immobility was essential to minimize the number of artefacts recorded. The patients were supervised during recording and all artefacts were identified and marked on the tracing (e.g. movement, coughing, straining or sighing)

Fifteen patients undergoing anterior resection for colorectal carcinoma were studied for 1 h per day for a median of 7 postoperative days, a cumulative total of 89 h of recording time. The tubes used across the anastomosis were made as described above except that two side holes were drilled near the tip and a further two 5 cm proximally, each pair orientated at 180° to the other pair (*Figure 1*). This assembly was passed *per anum* through a rigid sigmoidoscope immediately after the stapled anastomosis had been completed. Loops encircling each pair of holes to reduce mucosal contact were palpable through the bowel wall so the assembly could be accurately fixed across the anastomosis with a single full thickness catgut suture through an additional loop at the end of the assembly

All recordings were made synchronously, two channels 2 5 cm proximal and two channnels 2·5 cm distal to the anastomosis

Activity was defined as the presence of one or more colonic waves. Zero pressure was defined as that pressure recorded at the level of the top of the patient's mattress The hydrostatic pressure of the column of water in the perfused tubes above the level of the mattress and the weight of the anterior abdominal wall produced a baseline y axis deviation referred to as the resting pressure.

Waves of an amplitude of <10 mmHg were not included in the analysis because of the difficulty of differentiating low amplitude colonic waves from artefacts and the fact that the analogue–digital converter for each of the channels had different sensitivities at pressures of <10 mmHg.

The study protocol was approved by the West Birmingham Health Authority Ethical Committee.

Results

Control studies

The amplitude of 280 separate waves was recorded on four channels yielding a total of 1120 events. The mean of the four samples of each wave was calculated and the difference of each sample from this mean was determined These mean absolute deviations in mmHg were expressed as a percentage of all the samples, 64 per cent of the waves were within 2 mmHg and 96 per cent within 8 mmHg of their mean over the range 10–100 mmHg.

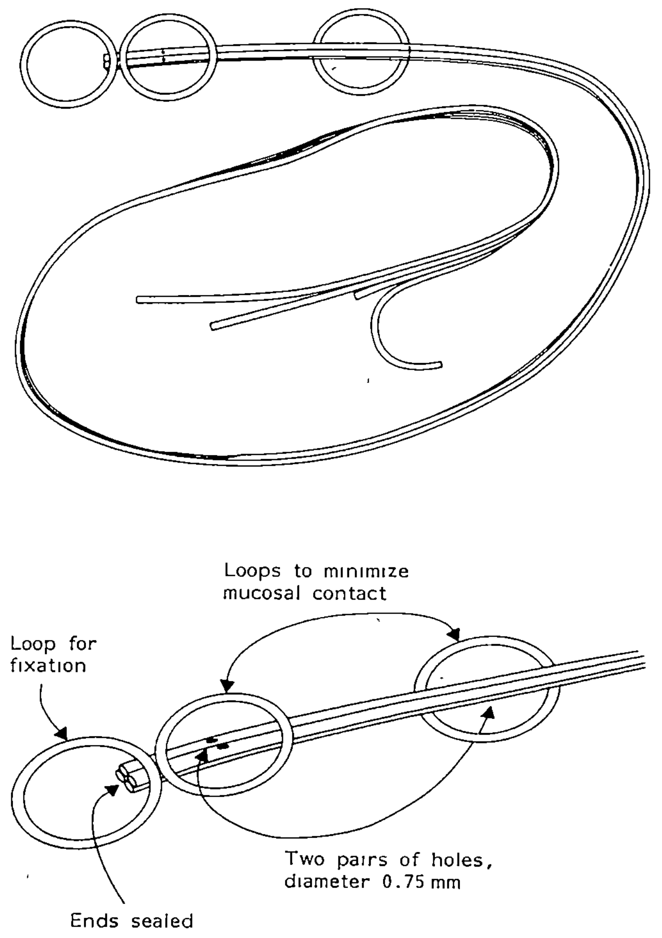
Loops to minimize mucosal contact
Loop for fixation
Two pairs of holes, diameter 0.75 mm
Ends sealed

Figure 1 *The tube assembly for detecting changes in pressure on either side of a left colonic anastomosis*

There was a wide variation between patients in the amount of activity recorded in terms of duration and amplitude despite the patients undergoing cholecystectomy having identical procedures and management. Patients undergoing herniorrhaphy had mean percentage duration of activity of 25 per cent on day 1 compared with only 10 per cent for the patients undergoing cholecystectomy.

Colonic resection studies

Patients undergoing anterior resection had a colonic ileus which lasted for 3–10 days and during this proximal and distal inactivity the intraluminal pressure remained within 6 mmHg of atmospheric pressure.

When activity returned the most common waveform was a simple wave, the shape of an isosceles triangle. The incidence of waves of different amplitudes was quantified as the frequency of occurrence of a wave of a given amplitude expressed as a percentage of all the waves. These results are shown in *Table 1* and are pooled from all waves recorded distal to the anastomosis on all the postoperative days; 68 per cent of these waves over 10 mmHg were <20 mmHg and 98 per cent had an amplitude <50 mmHg In the control group only 42 per cent were between 10 and 20 mmHg and 98 per cent were <80 mmHg.

The mean percentage time during which activity >10 mmHg was present at the anastomosis and in the controls is shown in *Table 2*. There was very little activity >10 mmHg at the anastomosis during the first 4 postoperative days compared with the controls The maximum amount of activity occurred on the eighth postoperative day, distal to the anastomosis and constituted 19 per cent of the recording time. The peak pressures recorded on this day were 25 mmHg proximal and 67 mmHg distal to the anastomosis. Proximal to the anastomosis there was very little activity recorded at any time during the postoperative period. The greatest amount of activity of an amplitude >10 mmHg occurred for only 2·6 per cent of the recording time on the fifth postoperative day.

Synchronous activity across the anastomosis was recorded in every patient at some time during the postoperative period. The peak amplitude of these synchronous waves was between 70 mmHg and 90 mmHg, but they were present for only 0·06 per cent of the recording time.

In four patients a different pattern of activity occurred; simple contractions with an isosceles waveform were consistently absent and were replaced by a sustained elevation in pressure which lasted for at least 2 min. These were often repetitive and lasted for 15–20 min and will be called tonic contractions. Their mean amplitude was 20 mmHg and the peak pressure was 45 mmHg. None was recorded during the first 3 postoperative days.

Discussion

Complete tube blockage was not a problem in this study because all patients had mechanical bowel preparation. Partial tube blockage caused an elevation in the baseline, a loss of respiratory artefact and a loss in fidelity of the recording of colonic activity. As simultaneous recordings were made on two channels at the same site, this artefact was easily recognized These and other artefacts were excluded.

When a manometer line was connected to the fine-bore tubes there was a rise in pressure which was the same on each postoperative day, suggesting that the intraluminal pressure was constant, in the absence of colonic activity.

Pneumatic pressure has been used to disrupt experimental anastomoses in animals[5] and the strength of an anastomosis is dependent upon the sutures during the first 2–3 days, thereafter fibroplasia becomes progressively more important and the bursting strength increases as new collagen is formed[6–9]. If mechanical forces played a major role in anastomotic disruption they would be most likely to produce

Table 1 *Frequency of occurrence of a wave of a given amplitude expressed as a percentage of all the waves*

Amplitude (mmHg)	Controls (%)	Patients (%)
10–19·9	42·5	68·0
20–29·9	22·8	19·0
30–39·9	12·6	8·5
40–49·9	6·4	2·3
50–59·9	5·1	0·3
60–69·9	4·8	0·3
70–79·9	4·2	0
80–89·9	1·4	1·2
90–99·9	0	0·3

Table 2 *Mean percentage activity >10 mmHg on each postoperative day*

Postoperative days	Controls ($n=10$, %)	Proximal to anastomosis ($n=15$, %)	Distal to anastomosis ($n=15$, %)
1	10	0	0
2	10	0	0
3	28	0·3	8
4	38	0·6	2
5	–	2·6	4·5
6	–	0·1	3·9
7	–	0·6	0·9
8	–	0·8	19
9	–	0	9·5
10	–	0·5	1

damage during the first 3 days. In this study no colonic activity in excess of 10 mmHg occurred on the first postoperative day and only one wave was recorded on day 2. On day 3 only 8 per cent of the distal recording was of waves >10 mmHg.

The maximal elevations in intraluminal pressure occurred on day 8 distal to the anastomosis and still constituted only 19 per cent of the recording time. As collagen formation is well advanced by this time, intraluminal pressure is unlikely to play a major role in anastomotic dehiscence.

Tonic contractions occurred from day 4 onwards in four patients. They lasted for up to 20 min and, although returning to baseline, this was for only a few seconds before another wave commenced. This degree of sustained pressure of 30 mmHg and up to 45 mmHg for 15–20 min has been shown to be capable of causing capillary stasis and ecchymoses[10].

Immediately after surgery it would seem unwise actively to stimulate the colon. Chaudhary and Truelove[11] showed that the cholinesterase inhibitor prostigmine increased the frequency and amplitude of colonic waves. Lewis observed an ileorectal anastomotic dehiscence as a result of neostigmine, prompting the retrospective study by Bell[12] who found a 36 per cent leak rate in those receiving neostigmine at the end of their ileorectal anastomosis compared with 4 per cent in a group who did not. In contrast, Whitaker[13] found no difference in the leak rates in 615 patients who had left colonic anterior resections whether neostigmine had been used or not In experimental work in dogs neostigmine caused intraluminal pressures of 75 mmHg. Whitaker observed in two animals that the effect of prostigmine was more marked distal to the anastomosis than proximal to it. During each contraction wave the mesenteric blood flow was reduced by 30–50 per cent and the effect was not entirely abolished by atropine.

In this study synchronous activity was recorded across the anastomosis on a number of occasions demonstrating patency but not identifying the origin of the contraction. The amplitude of the distal waves of this synchronous activity reached 90 mmHg, far exceeding the 46 mmHg maximum amplitude at the proximal site. The duration of activity distal to the anastomosis was up to 25 times greater than proximal. It is likely therefore that the contraction which produces the synchronous activity originates distally. The waveform of the synchronous activity usually resembled that recorded distal to the anastomosis but proximal activity alone had a more simple waveform.

A difference in activity across an anastomosis was noted by Parks[14] to be present at least 6 months after a left colonic resection for diverticular disease. He studied the motility patterns and the compliance of the colon proximal to the anastomosis and compared it with those without resections and normal controls. He stated, 'The observation of markedly increased activity in the rectum below the anastomotic line was of considerable interest. It seems that some inhibitory mechanism to rectal motility has been disturbed by operative intervention. The division of the pelvic mesocolon and blood vessels to the rectosigmoid region and also, possibly in some cases interference with the presacral fibres, may ablate part of the sympathetic supply to the upper rectum and thus account for the rectal hyperactivity'. Park's study suggests that the activity distal to the anastomosis is abnormally high rather than that the proximal activity is being inhibited.

Dinoso *et al.*[15] studied the basal motor activity of the distal colon and found a significant increase in the motor activity recorded at 15 cm from the anus compared with that recorded at either 20 or 25 cm. This difference was present whether the colon was unprepared or mechanically cleansed and an alternative explanation may be that the difference in activity recorded across the anastomosis simply represents the normal activity in the rectum compared with the normal but lesser activity in the sigmoid or descending colon.

An anastomosis is most vulnerable to an applied bursting pressure during the first 3 days. This study has shown that colonic activity in excess of 10 mmHg was not recorded during the first 2 postoperative days and constituted a mean of only 8 per cent of the recording time on the third day. There was no sustained elevation in pressure either proximal or distal to the anastomosis and no persistant pressure gradient across the anastomosis which lasted throughout the postoperative period. Intraluminal pressure is unlikely to play a major role in anastomotic dehiscence.

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Irreducible inguinal hernia in children below two years of age

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Eighty-five cases of irreducible inguinal hernia in children below 2 years of age were reviewed. Non-operative treatment was successful in 71 (84 per cent); 14 children required emergency surgery. The younger the child and the longer the duration of symptoms at presentation, the worse was the outcome of non-operative treatment. In 35 (41 per cent) children the diagnosis of inguinal hernia had been made before irreducibility. There is an increased incidence of postoperative complication associated with irreducibility, especially in preterm infants. Early diagnosis of inguinal hernia in young children and prompt referral for surgery is recommended.

Keywords: Inguinal hernia, irreducible, children

Inguinal hernia is the commonest congenital abnormality requiring surgical intervention in children. Irreducibility is a common reason for emergency admission. It complicates between 7 and 30 per cent of hernias and occurs most commonly in the first 6 months of life[1,2]. There is universal agreement among paediatric surgeons that attempts at manipulative reduction are both safe and effective when there are no signs of strangulation[3] Many children admitted to this unit with irreducible inguinal hernia had had a diagnosis of inguinal hernia made at an earlier time and had not been referred for elective surgery. In some cases there was also considerable delay in referral following the onset of symptoms. An experience of 85 infants aged 2 years or less with an admission diagnosis of irreducible inguinal hernia is presented.

Patients and methods

The notes of all children under 2 years of age admitted between 1984 and 1987 with the diagnosis of irreducible inguinal hernia were reviewed. Treatment policy consisted of gentle taxis with or without sedation and elevation. Children with a hernia that failed to reduce had emergency surgical reduction, those with successful reductions underwent later elective surgery.

Results

There were 85 children, 79 (93 per cent) boys and six (7 per cent) girls. Herniation was right sided in 69 (81 per cent), left sided in 13 (15 per cent), and bilateral in three (one side irreducible). Sixty-nine (81 per cent) were under 6 months of age (*Figure 1*). Thirty (35 per cent) had been born preterm. Referral was from a general practitioner in 47 (55 per cent) cases and from a district general hospital in 38 (45 per cent). Presenting clinical features were: pain in 40 (47 per cent), groin swelling in 32 (38 per cent), vomiting in 30 (35 per cent), constipation in 21 (25 per cent), irritability in 14 (16 per cent) and distension in two (2 per cent). The duration of symptoms at presentation ranged from 1 to 96 h, but half presented within 6 h. In 35 (41 per cent) infants the diagnosis of inguinal hernia had been made before the episode of irreducibility. In 20 the diagnosis had been made more than 3 weeks before and in seven more than 3 months previously. Thirty-one (36 per cent) had had attempted manipulative reduction which had failed before referral. In 10 (12 per cent) children the hernia had reduced spontaneously on arrival at this unit.

Fourteen children (16 per cent) had radiographs taken on admission. Of these radiographs, 12 showed fluid levels diagnostic of intestinal obstruction. Treatment consisted of gentle taxis in all 85 which was combined with sedation and elevation in 51. Successful reduction was achieved in 71 (84 per cent) patients who underwent later elective herniotomy within 72 h. Fourteen (16 per cent) had an emergency operation. In 13 this was because of failure of conservative management; one of these hernias reduced under general anaesthesia and was later repaired electively. The remaining patient had emergency surgery because a torsion of the testicle could not be excluded.

In those undergoing emergency surgery gentle taxis under anaesthesia reduced the hernia in six, the hernia sac being empty at operation. In four children the sac contained small bowel which in all cases was viable. In two children the sac contained ovary. In the remaining two children the sac contained testis,

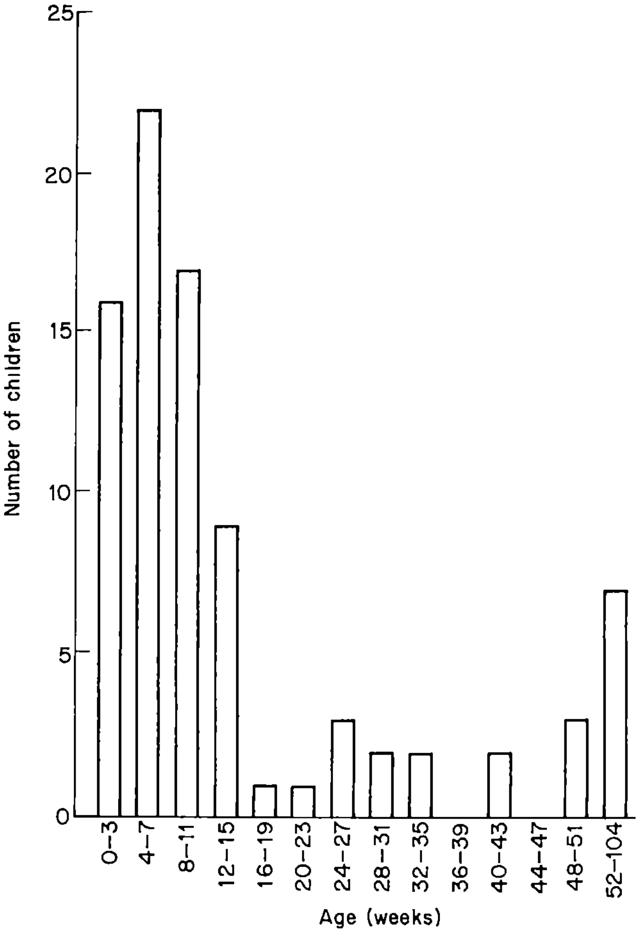

Figure 1 *Age distribution of 85 children <2 years old with irreducible inguinal hernia*

one ischaemic looking but viable and one infarcted. There was no evidence of torsion.

In those undergoing elective surgery the hernia sacs were empty. Five boys were noted to have bruised and discoloured testicles at operation. There were four immediate postoperative complications consisting of one primary haemorrhage in a child with idiopathic thrombocytopenia and three respiratory complications, all of which occurred in preterm infants who had required emergency surgery. Those children needing emergency surgery had a longer duration of symptoms (mean(s.d.) 34(36) h) than those undergoing elective surgery (mean(s.d.) 12(13) h). The average age of children undergoing emergency surgery was 12 weeks and of those having elective surgery 19 weeks.

Discussion

The incidence of inguinal hernia in children is between 0·8 and 4·4 per cent[3]. Approximately one-third of children with inguinal hernia are less than 6 months of age at the time of operation. Irreducibility complicates between 7 and 30 per cent of hernias[1,2,4] with 69 per cent of episodes of irreducibility occurring in the first year of life. The incidence of inguinal hernia in the preterm baby is highest of all and, although the exact incidence of irreducibility in this group is difficult to determine, in the present series 35 per cent of those children with irreducible hernias were born preterm This is in keeping with reports from other groups[5,6].

Gentle taxis successfully reduced 84 per cent of hernias. This is similar to other reports[2,4,5,7,8] Although unsuccessful attempts at reduction had been made before referral in 31 patients, in most cases reduction was achieved in this unit. The reason for this may be that the authors were more aware of the relative safety and efficacy of non-operative management and of the technical difficulties of urgent surgery than the referring doctors It is likely that persistence (being prepared to take as long as 40 min to reduce a hernia) is associated with success. The presence of signs suggesting bowel infarction, such as marked hernia tenderness, erythema and systemic upset in the child, should preclude attempted hernia reduction. Although 12 of the 14 patients who had radiographs had evidence of intestinal obstruction, this finding did not affect management This investigation is no longer performed for irreducible inguinal hernia in this unit.

Six of the 85 children were girls, two of whom failed to respond to non-operative treatment. Although the overall incidence of inguinal hernia is much lower in girls the incidence of irreducibility is probably higher[4]. The ovary is commonly found in the hernial sac. This can be difficult to reduce and may undergo torsion[9,10]

Two important factors that influenced the success of attempted reduction were the duration of symptoms at presentation and the age of the child. The longer the duration of symptoms at presentation and the younger the child the higher the incidence of non-reduction. Early referral is warranted.

There was no case of intestinal infarction in this series. The incidence is generally accepted to be very low[4,10] Infarction of the testicle in children with irreducible hernia has been well reported[11]. This series contained one case of infarction without torsion and six bruised and discoloured testicles.

Those children who had successful reduction were operated on within 72 h on routine lists. It is important for the child to remain in hospital for at least 24 h following reduction as serious complications may still occur even after straightforward reduction[12].

Of the children in this series, 41 per cent had a known pre-existing hernia; in over half of these the hernia had been present for more than 3 weeks and their emergency admission was potentially avoidable Early diagnosis and surgery must be the goal if we are to reduce the incidence of irreducibility.

There were immediate postoperative complications in four children. Three of these occurred in preterm infants and were potentially serious. This has been observed by others[5,13].

The policy of this unit is to operate on all preterm babies with inguinal hernias just before their discharge from the special care baby unit. If preterm babies develop a hernia after discharge they are operated on soon after diagnosis. This policy has also been advocated by Rescorla and Grosfeld[5] It should prevent irreducibility and its subsequent increased morbidity. Perhaps the criteria used for preterm infants should be extended to all children under 2 years of age.

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Effect of hydrocele on testis and spermatogenesis

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One hundred and twenty cases of big unilateral hydrocele of the tunica vaginalis testis have been studied to ascertain the effect on the structure and function of the testis, taking the normal side as control. There was no pressure effect from the hydrocele on the structure of the testis in 70 per cent, a flattening of testis in 22 per cent, and atrophy of testis in 8 per cent of cases. There was partial arrest of spermatogenesis in 10 per cent and total arrest of spermatogenesis in 8 per cent of cases. The remaining 82 per cent showed normal spermatogenesis.

Keywords: Hydrocele, spermatogenesis, testis

Hydrocele of the tunica vaginalis testis is a common condition, especially in tropical countries like India. The incidence is high in the coastal districts of Orissa, mostly as a result of filariasis[1]. If left untreated the hydrocele enlarges and causes great discomfort and interference with physical and sexual activities.

In spite of being such a common affliction, little work has been done to study the effects of hydrocele on the structure and function of the testis. It has been suggested that a large and long-standing hydrocele causes certain anatomical changes, such as atrophy, and hampers spermatogenesis. This may be caused by both direct pressure on the testis and interference with the blood supply from oedema within the tight fibrous enclosure of the tunica vaginalis[2]. The following study was undertaken on the effects of hydrocele on the testis.

Patients and methods

The study was carried out on 120 men with large unilateral hydroceles. Bilateral hydrocele was excluded from the study. The age of the patients ranged from 30 to 40 years. All were operated on under spinal or general anaesthesia. After evacuation of hydrocele fluid a testicular biopsy was taken through a 4 mm square incision in the tunica albuginea. The extruded testicular tissue and a small portion of tunica albuginea was excised with scissors. A biopsy was also taken from the opposite testis which served as a control. Tissues were placed in freshly prepared Bouin's solution. The tunica and the scrotal layers were sutured. At the time of operation the volume of hydrocele fluid and any gross change in the testis such as atrophy, flattening, thickening of tunica vaginalis or epididymis were recorded.

Paraffin sections of biopsies were cut and stained with haematoxylin and eosin. Special staining was also done to demonstrate basement membrane thickening and fibrosis.

Results

The majority of patients were 20 to 40 years old (median 30 years) with a hydrocele of 2–5 years' duration (median 4·8 years). Ninety-three patients (78 per cent) presented with more than 300 ml of fluid in the tunica vaginalis testis (median 558 ml).

On the affected side there was atrophy of testis in 8 per cent and flattening of the testis in 22 per cent of cases. Thickening of the epididymis and cord was observed in 15 (12 per cent) and 21 (18 per cent) of cases respectively.

Biopsies from the control side showed essentially normal spermatogenesis. On the affected side, 10 per cent had partial arrest of spermatogenesis at the spermatocyte level (*Figure 1*) and 8 per cent had total arrest of spermatogenesis (*Figure 2*). The remaining 99 (82 per cent) biopsies from the affected side showed normal spermatogenesis (*Table 1*).

Large numbers of disorganized spermatogenic cells were seen in the tubules of 42 per cent, and interstitial cell fibrosis was seen in 85 per cent of biopsies from the affected side. Similar changes occurred in 8 per cent of the control side. Thickening of the basement membrane was seen in 78 per cent of biopsies from the affected side and in 12 per cent of biopsies from the control side. Thickening of the tunica albuginea and tunica vaginalis was seen in 85 per cent of biopsies from the affected side (*Table 1*). Leydig cells were unchanged on both sides.

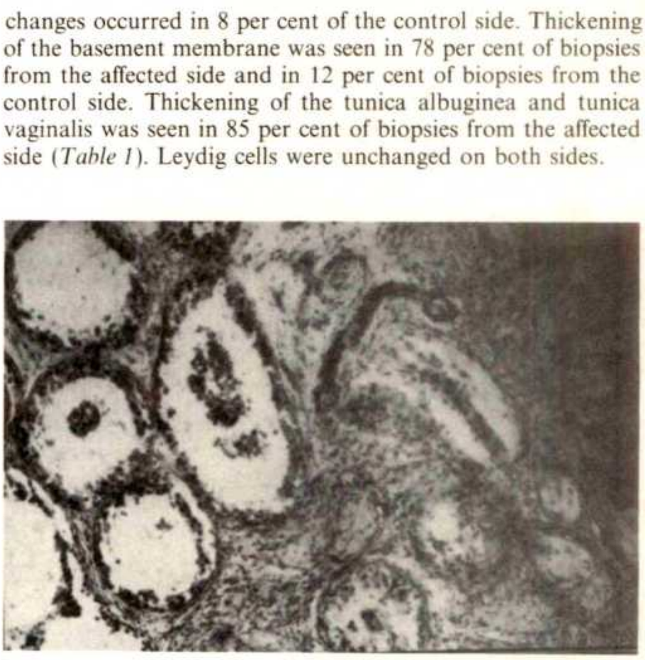

Figure 1 *Histopathological changes in the testis (original magnification × 100). Interstitial fibrosis, thickening of the basement membrane of the tubules and complete arrest of spermatogenesis at the spermatogonia level are seen. One tubule shows partial arrest*

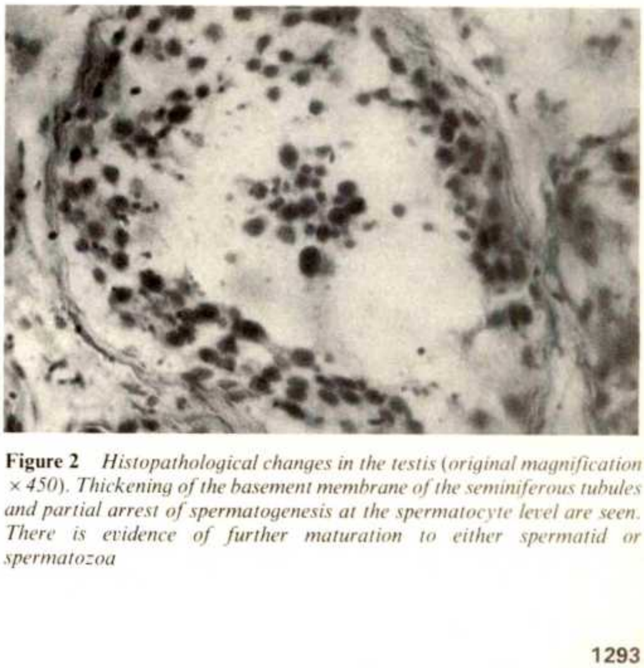

Figure 2 *Histopathological changes in the testis (original magnification × 450). Thickening of the basement membrane of the seminiferous tubules and partial arrest of spermatogenesis at the spermatocyte level are seen. There is evidence of further maturation to either spermatid or spermatozoa*

Table 1 *Histological comparison of testes affected by hydrocele with normal (control) testes*

	Hydrocele	Control
Histology	No. of cases (%)	No. of cases (%)
Normal histology	18 (15)	96 (80)
Tunica vaginalis thickening	102 (85)	0 (0)
Tunica albuginea thickening	102 (85)	0 (0)
Basement membrane thickening	93 (78)	15 (12)
Interstitial fibrosis	102 (85)	9 (8)
Disorganization and sloughing	51 (42)	0 (0)
Partial arrest of spermatogenesis	12 (10)	0 (0)
Total arrest of spermatogenesis	9 (8)	0 (0)

Discussion

The adverse effect of a large unilateral hydrocele on testicular function is not widely known and certainly not well documented. Bhatnagar *et al.* have reported that hydrocele has no effect on the testis except an increase of fibrous tissue in the tunica and interstitial areas[3]. However, Dey observed an arrest of spermatogenesis and consequent testicular atrophy as a result of fluid pressure in the tunica vaginalis[4]. Arrest of spermatogenesis may also be caused by pressure on the blood supply of the testis from oedema within a tight fibrous sheath enclosing the tunica vaginalis[2]. Saifee *et al.* observed arrest of spermatogenesis when the amount of fluid within the tunica was considerable and under tension[5]. In the present series, arrest of spermatogenesis was apparently caused by a large quantity of fluid under tension. The possibility that such an arrest might be due to increased intrascrotal temperature retarding spermatogenesis needs further investigation.

Disorganization and sloughing was noted in 42 per cent of cases in this series, which is similar to the findings of Dyke[6]. These features might be due to obstruction of the vas or epididymis from fluid pressure.

Bhatnagar *et al.* reported thickening of the basement membrane in only 25 per cent of cases[3] but in the present study this feature was noted in 78 per cent of the affected sides and 12 per cent of the control sides.

The tunica vaginalis and tunica albuginea were thickened in 85 per cent of cases in our series which corresponds with the findings of Bhatnagar *et al.*[3]. Interstitial fibrosis was present in 85 per cent of the affected sides and 8 per cent of the control sides. It may be due to prolonged contact with protein-rich fluid inside the tunica vaginalis.

It would seem that big hydroceles of the tunica vaginalis testis of long duration impair spermatogenesis and may lead to subfertility or infertility. A direct relationship was observed between duration of the hydrocele and testicular change. The longer the duration of the hydrocele and the larger its size, the greater the pressure effect and pathological change.

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New isotopic technique for detecting prosthetic arterial graft infection: ^{99m}Tc-hexametazime-labelled leucocyte imaging

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Early and accurate detection of prosthetic arterial graft infection is important because this serious complication of vascular surgery carries high morbidity and mortality rates. This report describes the use of a new method of isotopic imaging to detect graft infection using ^{99m}Tc-hexametazime-labelled leucocytes. Seventeen patients with potentially infected arterial grafts were imaged in addition to routine investigations but were managed according to our normal surgical practice. ^{99m}Tc-imaging was positive in eight patients with proven graft infection and falsely positive in one patient with a groin haematoma (89 per cent specificity). There were no false negatives (100 per cent sensitivity) after an average follow-up of 6 months (range 3–9 months). This technique has proved a reliable and rapid method of confirming graft infection.

Keywords: Arterial graft infection, leucocyte labelling, ^{99m}Tc-hexametazime leucocyte imaging

Infection of prosthetic arterial grafts is a serious complication with a reported incidence of 1·3–6 per cent[1] and high morbidity and mortality. Significant risk factors for infection include groin dissection and graft revision. Early and aggressive surgical treatment with removal of infected material has been the recommended method of management[1] though some success has been reported with less radical treatment[2].

A high index of suspicion and accurate investigation are therefore required to allow early detection since the presentation is often unclear and may be long delayed after the original graft implantation. Investigations currently available are often unreliable[3–6] but computed tomography[7] and ^{111}In-labelled leucocyte scintigraphy[8,9] are claimed to be the most accurate.

Improved means to detect graft infection reliably continue to be sought. A new method of leucocyte labelling using technetium-hexametazime (^{99m}Tc-HMPAO-WBC, Ceretec, Amersham International PLC, Amersham, UK) has been described for use in a variety of infective conditions and has several advantages over current isotopic techniques[10].

The use of ^{99m}Tc-HMPAO-WBC in detecting vascular graft infection is not yet widely practised[11,12]. This paper describes the use of ^{99m}Tc-HMPAO-WBC scintigraphy in the investigation of patients with suspected infection of arterial prostheses.

Patients and methods

Seventeen patients with suspected prosthetic arterial graft infection have undergone imaging with ^{99m}Tc-HMPAO-WBC in addition to appropriate routine investigations. Management of the patients proceeded according to the normal practice in this centre to allow assessment of the relative value of this new technique.

There were ten men and seven women with an average age of 66 years (range 50–79 years). There were ten aortic, two axillofemoral, two iliopopliteal and three infrainguinal grafts; 14 had involved groin incisions and nine had involved graft revision. The graft material was Dacron® (E.I. du Pont de Nemours and Co., Wilmington, Delaware, USA) in 13 patients and polytetrafluoroethylene (PTFE) in four patients with distal grafts.

Confirmatory microbial cultures were obtained from graft material, blood or wounds wherever possible. Details of the patients and modes of presentation are shown in *Tables 1* and *2*. Clinical evidence, after surgical intervention or follow-up, was taken to be the final arbiter of graft infection against which the result of ^{99m}Tc-HMPAO-WBC imaging was compared.

^{99m}Tc-HMPAO-WBC preparations were made using a method based on that of Danpure[13] using 50 ml of blood taken on the morning of scintigraphy. The blood was sedimented and centrifuged to obtain a leucocyte-rich sample which was suspended in plasma and incubated with ^{99m}Tc-HMPAO before re-injection into the patient. The injected activity was approximately 200 MBq (radiation dose approximately 3·5 mSv) with 94 per cent associated with leucocytes[13].

Imaging was undertaken at 2–3 h after re-injection using a General Electric Medical Systems 400AC γ-camera (IGE Ltd., Slough, UK) and low energy collimator.

Table 1 *Details of patients with negative ^{99m}Tc-HMPAO-WBC imaging*

Site of graft	Graft material	Presentation (days in hospital)	Progress (months of follow-up)
Aortoaortic	Dacron	Postoperative pyrexia, perigraft collection on sonar (36)	Settled after removal of venous cannula (9)
Aortobifemoral	Dacron	Acute ischaemia and cellulitis (19)	Settled after embolectomy and fasciotomy (9)
Aortobifemoral	Dacron	Pus in groin, graft occluded (28)	Distal graft excised, healed (8)
Aortobifemoral	Dacron	General malaise and anaemia (15)	Settled, anaemia treated (6)
Aortobifemoral	Dacron	Groin wound infection (13)	Healed with iodine dressings and antibiotics (4)
Aortobifemoral	Dacron	Blocked graft, groin seroma (12)	Distal graft excised, healed (3)
Iliopopliteal	PTFE	Popliteal wound infection (19)	Healed with iodine dressings and antibiotics (5)
Femoropopliteal	Dacron	Groin seroma (31)	Drainage/excision, seroma recurred (3)

PTFE, polytetrafluoroethylene

Table 2 *Details of patients with positive ^{99m}Tc-HMPAO-WBC imaging*

Site of graft	Graft material	Presentation (months after graft inserted)	Progress (days in hospital)
Aortobifemoral + cholecystectomy	Dacron	Postoperative septicaemia and renal failure (1)	Died, renal infarction and abscess (14)
Aortobifemoral	Dacron	Groin abscess, recurred after partial excision of graft (72)	Graft excised, replaced with vein (57)
Aortobifemoral	Dacron	Groin abscess and fever, recurred after partial excision of graft (156)	Graft excised (found within jejunum) (55)
Aortobifemoral	Dacron	Pericolic and recurrent groin abscesses (3)	Graft excised, Hartmann procedure, axillo-femoral bypass (75)
Axillobifemoral	Dacron	Groin and trunk abscesses (17)	Graft excised (162)
Axillobifemoral	Dacron	Recurrent groin and trunk abscesses (28)	Graft excised (209)
Iliopopliteal	PTFE	Groin sinus and bleeding (40)	Graft replaced (75)
Femoropopliteal	PTFE	Septicaemia and metastatic abscesses (1)	Died, no surgery (26)
Femorotibial	PTFE	Calf wound infection (12)	Graft excised, late re-graft (46)

PTFE, polytetrafluoroethylene

Results

^{99m}Tc-HMPAO-WBC imaging was positive in nine of the 17 patients. In five patients uptake was localized (*Figure 1*): extensive uptake along the graft was seen in the remaining four scans (*Figure 2*). There were two patients with a graft–enteric erosion or fistula (*Table 2*, patients 3 and 4).

No false negative scans (100 per cent sensitivity) were apparent after an average follow-up of 6 months (median 6, range 3–9 months). There was one false positive scan (89 per cent specificity) due to a groin haematoma. The patient, referred to this centre for dialysis, had septicaemia and renal failure following aortobifemoral reconstruction for aneurysm with simultaneous cholecystectomy. There was no evidence of graft or groin infection at autopsy.

Positive microbial cultures were obtained from grafts in eight patients, all with positive ^{99m}Tc-HMPAO-WBC scans. *Staphylococcus aureus* was implicated in seven of these, with mixed cultures in four (*Table 3*). Positive cultures, other than from grafts, were also found in patients with an infected central venous cannula and in two with wound infections. These patients had negative scans. Negative scans were also obtained in four patients with negative cultures and no further evidence of graft infection during follow-up.

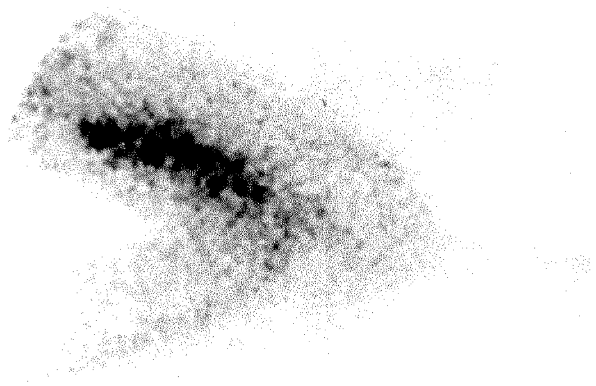
One patient, while on antibiotic treatment, had a negative culture despite a positive Gram stain of pus from around the graft. In this patient the graft infection was an incidental finding during groin re-exploration for an occluded aortobifemoral bypass. The clinically infected distal part of the occluded limb of the graft was excised and the ^{99m}Tc-HMPAO-WBC scan (negative result) was subsequently undertaken to exclude infection in the remaining graft before proceeding with revascularization.

One patient with a negative scan underwent surgical exploration of a groin swelling for which histology and culture confirmed a non-infected seroma. One other patient with a negative scan had groin re-exploration for graft occlusion and the graft was found to be surrounded by granulation tissue and serous fluid. Cultures from excised graft material, tissue and fluid were all negative and the wound healed satisfactorily.

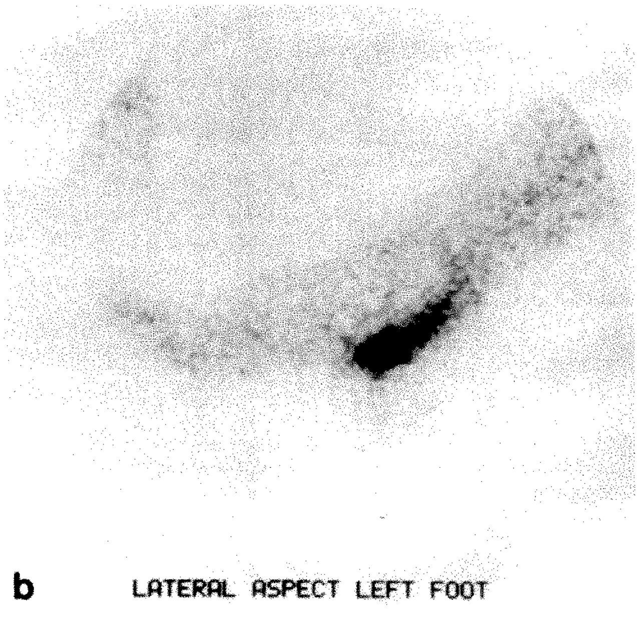
Tables 1 and *2* confirm the serious nature of graft infection. Average stay in hospital for affected patients was 80 days (median 56, range 26–209 days) compared with 21 days (median 19, range 12–36 days) for patients without graft infection. Two of the patients with infected grafts died. The average delay from graft implantation to presentation with graft infection was 39 months (median 22, range 1–156 months).

Discussion

In this series, ^{99m}Tc-HMPAO-WBC imaging correctly identified all of the patients with infection of grafts proven at surgery. None of the patients with negative scans developed



a MEDIAL ASPECT LEFT LEG



b LATERAL ASPECT LEFT FOOT

Figure 1 *^{99m}Tc-HMPAO-WBC scan showing localized uptake* **a** *at the knee and* **b** *at the ankle in a patient with a distally infected femoropopliteal graft and ankle abscess*

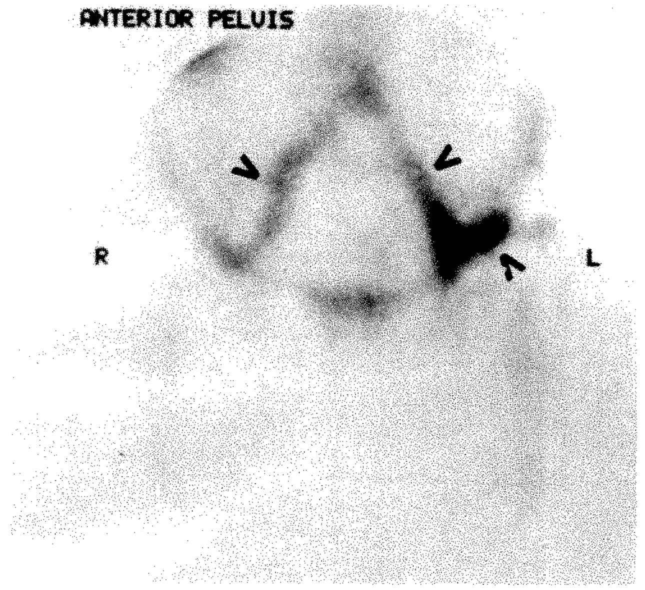


Figure 2 *^{99m}Tc-HMPAO-WBC scan showing generalized uptake outlining the limbs of an infected aortobifemoral graft and an abscess in the left groin (all arrowed)*

Table 3 *Details of grafts with infection*

Site of graft	Graft material	^{99m}Tc-uptake	Organisms
Aortobifemoral	Dacron	Left and right limbs of graft	*Staphyloccocus aureus*, *Haemophilus*
Aortobifemoral	Dacron	Whole of graft	*Escherichia coli*, *Streptococcus*, *Bacteroides*, *Candida*
Aortobifemoral	Dacron	Whole of graft	*S. aureus*, *E. coli*, *Morganella*, *Streptococcus*
Axillobifemoral	Dacron	Whole of graft	*S. aureus*
Axillobifemoral	Dacron	Localized over bifurcation of graft	*S. aureus*, *Proteus*, *E. coli*, *Enterococcus*
Iliopopliteal	PTFE	Lower part of graft	*S. aureus*
Femoropopliteal	PTFE	Lower part of graft and ankle abscess	*S. aureus*
Femorotibial	PTFE	Whole of graft	*S. aureus*

PTFE, polytetrafluoroethylene

further signs of graft infection on follow-up. The one false positive result gave an overall accuracy of 94 per cent which compares well with other techniques[3–9].

Whether computed tomography or ^{111}In-scintigraphy is currently the better investigation for graft infection is controversial[9,14,15]. Tomography is not specific for infection. The definitive tomographic sign of small bubbles of gas around the graft is present in only a third of cases[15] and gas may normally be present in the early postoperative period[16]. This low sensitivity may reflect the predominance of non-gas-producing organisms in graft infection.

Scintigraphy may fail to show chronic low-grade infection[17] but this problem was not recognized in our series. Early postoperative ^{111}In imaging within 14 days of surgery may show activity around uninfected grafts[18] and ^{99m}Tc-HMPAO-WBC imaging should share this problem. However, no such falsely positive activity was found in this series with the earliest postoperative scans at 5, 8 and 23 days.

Scintigraphic false positives have also been reported with platelet contamination, false and inflammatory aneurysms, haematoma, acute inflammatory conditions, enteric anastomoses, renal allografts and accessory splenic tissue[9,17,19,20]. One groin haematoma showed ^{99m}Tc-HMPAO-WBC uptake in our series but this patient had no clinical or autopsy evidence for graft infection. The results of investigations should always be interpreted in the light of clinical information.

Compared with other isotopic techniques, ^{99m}Tc-HMPAO-WBC imaging has many advantages and few disadvantages[10,20]. The radioisotope ^{99m}Tc is relatively inexpensive, readily available, and has ideal imaging properties. However, the current cost of hexametazime renders overall cost similar to ^{111}In-leucocyte imaging. Both ^{99m}Tc and ^{111}In-leucocyte labelling require labour-intensive and skilled preparation.

The radiation dose from 200 MBq ^{99m}Tc-HMPAO (3·5 mSv) is only half that of 12 MBq ^{111}In-oxine (6·8 mSv)[10] and the higher activity permitted in ^{99m}Tc-labelling allows tolerance of suboptimal labelling efficiency. There is some evidence that ^{111}In-oxine may decrease leucocyte cell function[21] resulting in reduced diagnostic sensitivity. The nuclear disintegration characteristics of ^{111}In may also result in radiation-induced cell damage[22]. There is no evidence to date for either of these problems with ^{99m}Tc-HMPAO.

^{99m}Tc-HMPAO-WBC imaging must be carried out within 4 h of injection to avoid confusion due to bowel uptake but this means that an early result is available without decreased sensitivity of the test. Other isotopic imaging results may require up to 48 h. The early bowel uptake with ^{99m}Tc-HMPAO-WBC suggests that ^{111}In-imaging may theoretically be better for detecting enteric fistulae but this remains to be proven in clinical practice.

Isotope imaging allows the detection of other infective sites which may have a bearing on patient management. Localized and generalized graft uptake are also differentiated allowing for localized intervention with reduced risk[2]. The case of patient 3 in *Table 1* illustrates local treatment; only the distal part of one limb of an aortobifemoral graft was excised and this patient has remained free of trouble during 8 months follow-up. Serial imaging may be used to confirm satisfactory treatment, local or radical.

^{99m}Tc-HMPAO-WBC imaging has proved a rapid and reliable method of confirming graft infection. Its accuracy compares well with that of other methods and it has several advantages compared with other isotopic techniques. The test differentiates localized and generalized graft infection and detects other relevant pathology.

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Buerger's colour

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Cyanosis of the hands and feet in Buerger's disease is known as 'Buerger's colour'. This characteristic skin colour is produced by the subpapillary venous plexus. The reactions of the subpapillary venous plexus in patients with Buerger's disease were observed by analysing the fractional blood volume of tissue using a visible light reflective spectrophotometer. Capillary morphology was investigated using an intravital video-microscopic system. Twenty-seven subjects, comprising 13 normals and 14 patients with Buerger's disease, were studied. In the nailbeds of patients with Buerger's disease, an increase in the number of loops, cyanotic colour change and dilatation were observed. In this condition there was incompetence of venular tonus and regurgitation at venular valves. Buerger's colour is probably due to excessive congestion of venous blood in the subpapillary venous plexus which is produced by these mechanisms.

Keywords: Buerger's disease, reflective spectrophotometer, intravital video-microscopic system, subpapillary venous plexus

Leo Buerger described a segmental occlusive vascular disease in 1908 with distinctive pathological and clinical features[1]. Buerger's disease, thromboangiitis obliterans, has been defined as an idiopathic, segmental, inflammatory, and recurrent occlusive disease which primarily affects the small or medium-sized arteries and veins of the extremities. The hands and feet of patients with arteriosclerosis obliterans are pale, whereas those of patients with Buerger's disease are cyanotic. This cyanosis of the hands and feet is known as 'Buerger's colour'. There are small pools of blood beneath the skin in the subpapillary venous plexus. The pinkish colour of the skin is caused by this network of small thin-walled vessels, which is about 1 mm below the skin surface.

The reactions of the subpapillary venous plexus in Buerger's disease were studied by observation of the fractional blood volume of tissue using a visible light reflective spectrophotometer[2]. Capillary morphology was also investigated using an intravital video-microscopic system (IVVMS)[3].

Patients and methods

Twenty-seven subjects, comprising 13 normals and 14 patients with Buerger's disease, were studied. The 13 normal subjects (21 lower extremities) were all men (age range 39–62 years, mean 48·2 years). The 14 patients with Buerger's disease (25 lower extremities) were also all men (age range 27–60 years, mean 44·8 years). The degree of circulatory impairment in all the patients was Fontaine's stages I or II. All patients with Buerger's disease and all normal subjects were smokers. The 13 normal subjects were hospitalized for conditions other than cardiovascular disease and results of physical examination and investigation were normal. The ankle and brachial systolic pressures were measured by the Doppler method and the ankle:brachial pressure ratio was greater than 1·0 in all cases.

The 14 patients with Buerger's disease had no evidence of heart disease which could be responsible for arterial emboli, an absence of aortoiliac occlusive disease, normal serum cholesterol levels, and no evidence of arterial calcification on radiography[4,5]. The radiological feature[6,7] of these 14 patients was multiple segmental arterial involvement ('skip lesions') in ten cases (71 per cent), tapered occlusions and filum terminale aspect in distal arteries in six cases (43 per cent), and tortuous or corkscrew-type collaterals in nine cases (64 per cent).

Reflective spectrophotometry[2] was performed with a biospectroanalyser composed of a 300 W xenon lamp light source, Czerny-Turner grating system with pulse motor, and two bundles of quartz glass optical fibres of 0·5 cm diameter. A microprocessor-controlled photodetector array was used to sample four specially selected wavelengths within a short time interval. The maximum velocity of scanning was 500 nm/0·5 s, and the range of absorbancy was ±2 optical density. The sampling area was the subpapillary venous plexus because the depth from which reflectance was received was about 1·0 mm from the skin surface of the sole (*Figure 1*). Scanning used light reflectance at four specially selected wavelengths, including two average oxy- and deoxyhaemoglobin equilibrium points (586 and 569 nm) and the peaks in the spectra of oxyhaemoglobin and deoxyhaemoglobin (577 and 560 nm), with reference to time (*Figure 2*).

These observations were performed under five different sets of conditions. In the first stage, the baseline optical density was obtained from the skin of the sole. Pressure was then applied to the skin using the tip of the optical fibre to squeeze blood out and the lower extremity was tilted up for 10 s. In the second stage, the skin of the sole was scanned for 40 s without any compression to observe changes in the volume of the plexus with upward tilting of the lower extremity. In the third stage, the skin of the sole was observed during inflation of an ankle cuff for 50 s with upward tilting of the lower extremity, to observe changes in volume of the venous plexus without arterial inflow. In the fourth stage, observation was performed with the lower extremity tilted downward and the ankle cuff inflated for 50 s to observe gravitational changes in the volume of the venous plexus. The fifth stage was a 50 s observation period without any compression and with the lower extremity tilted downward, to detect any increase in volume of the plexus due to reactive hyperaemia. Kubelka and Munk's equation[8–10] was utilized to calculate the fractional blood volume.

Observation of the capillary morphology in the nailbed was performed using IVVMS[3]. The IVVMS system utilized a stereomicroscope with a 3·5 × objective lens and a 20 × eye lens. The light

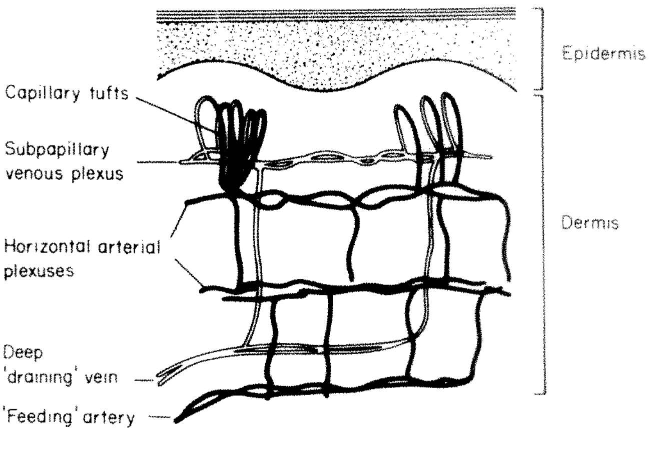

Figure 1 *A diagram to show the normal arrangement of the vessels in the dermis*

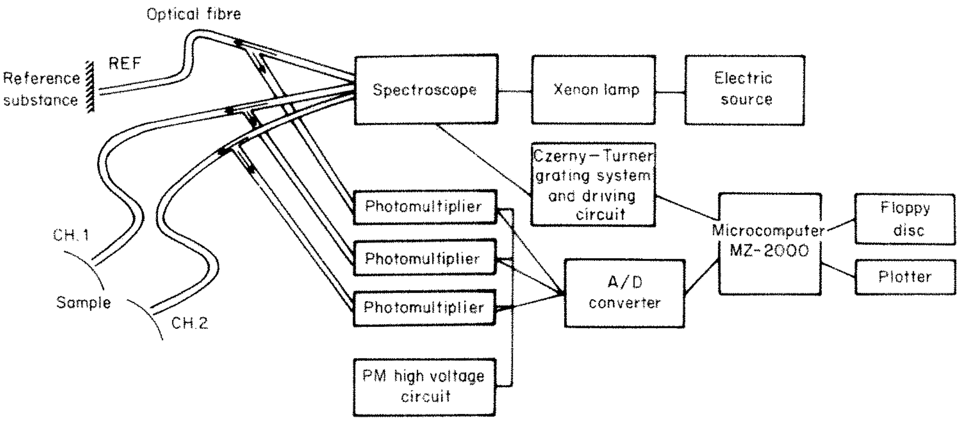

Figure 2 *Block diagram of the biospectroanalyser*

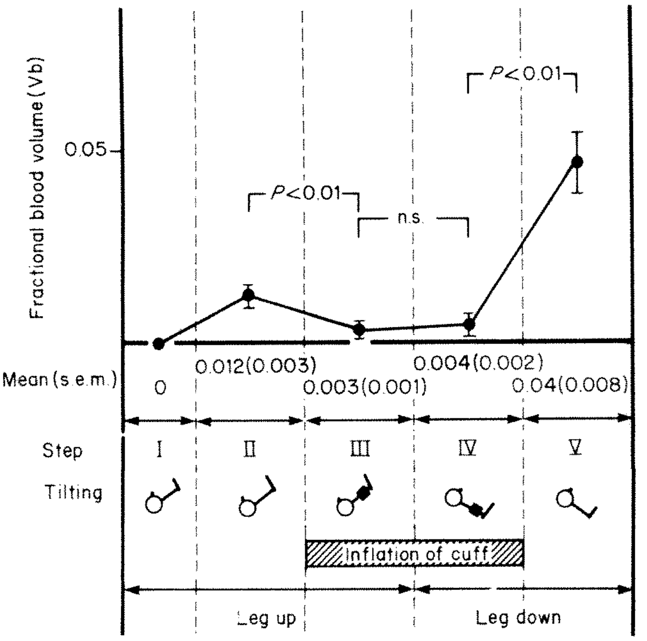

Figure 3 *Sequential changes in fractional blood volume (Vb) observed in normal subjects*

source was a non-heating 6 V, 15 W bulb. Total magnification was 70× on 35 mm film and 270× on a 20 inch colour TV monitor.

Statistical analysis

Results are expressed as the mean(s.e.m.). If statistical significances were calculated using F values, group comparisons were made using Student's t test. Differences were regarded as significant when $P<0{\cdot}05$.

Results

In normal subjects, there were significant differences between mean fractional blood volume in the second and third stage ($P<0{\cdot}01$) and between that in the fourth and fifth stage ($P<0{\cdot}01$), whereas there was no significant difference between mean fractional blood volume in the third and fourth stage (*Figure 3*). There was a significant difference between mean fractional blood volume in the fourth and fifth stage in the patients with Buerger's disease ($P<0{\cdot}01$). There was no significant difference between mean fractional blood volume of normal subjects and that of the patients with Buerger's disease in the second stage, whereas there were significant differences between the normal subjects and the patients with Buerger's disease in the third ($P<0{\cdot}01$), fourth ($P<0{\cdot}05$) and fifth stage ($P<0{\cdot}01$) (*Figure 4*).

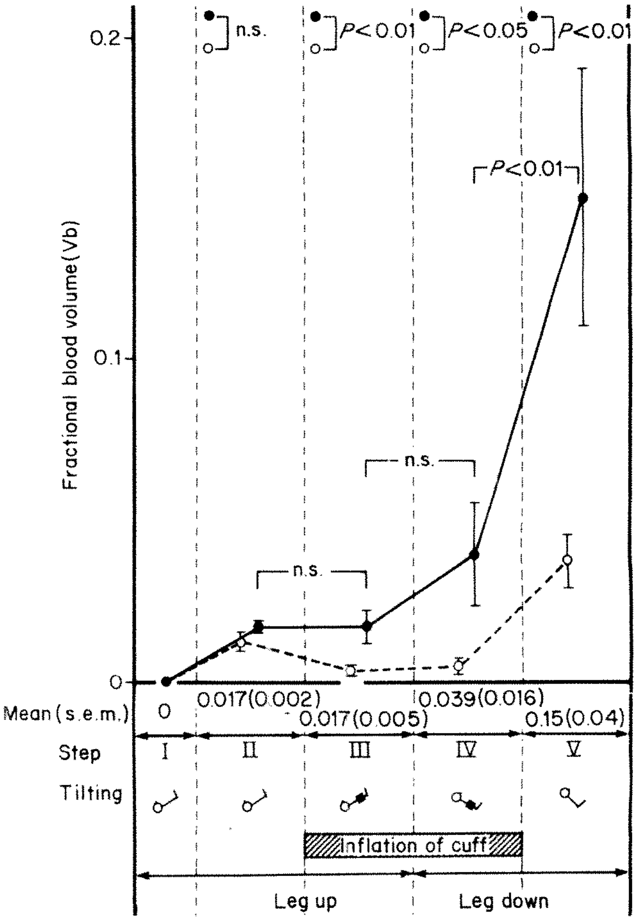

Figure 4 *Sequential changes in fractional blood volume (Vb) observed in patients with Buerger's disease (——) compared with normal subjects (– – – –)*

In the nailbeds of normal subjects generally only the crest between the arterial and venous limb of the capillary loops could be visualized by IVVMS. Capillary loops were regular and blood flow in the loops was normal. However, in Buerger's disease, an increase in the number of loops, cyanotic colour changes, and dilatation were observed. Irregular rows of capillaries were also observed (*Figure 5*).

Discussion

The absorbance of haemoglobin depends on the blood volume of local tissue and average oxygen content in the circulating

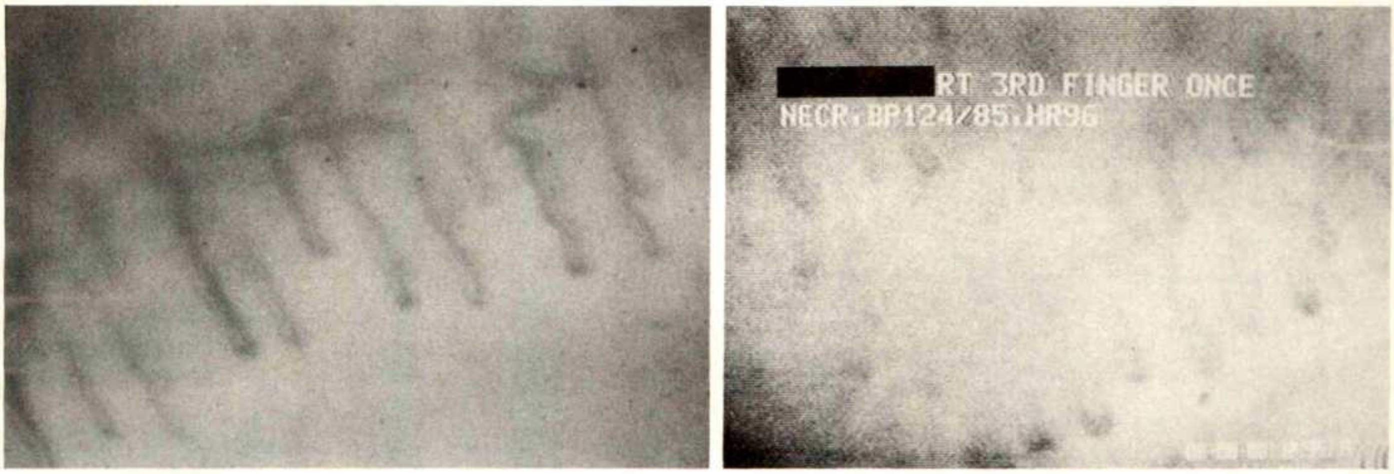

Figure 5 *(left) Healthy 22-year-old female; regular capillary loops and normal blood flow in the capillary loops* (× *180*). *(right) Buerger's disease in a 52-year-old male; cyanotic colour changes and dilated capillary loops in a finger which previously suffered necrotic change* (× *180*)

blood. Fractional blood volume in various tissue layers is unknown and can only be estimated roughly. If the fractional blood volume can be estimated by application of Kubelka–Munk's photon diffusion theory[8–10] to living tissue, the fractional blood volume value obtained at the isobestic wavelength of 586 nm should be equal to that obtained at the other isobestic wavelength of 569 nm. Skin differs in its microscopic scattering properties compared with its absorption. For simplicity, however, the scattering constant was assumed to be unity. This might be why there was a correlation between fractional blood volume and the ratio of the absorption constant to the scattering constant (αt), and also why there were different regression lines between fractional blood volume and αt for each subject[2]. It appeared that the volume of the subpapillary venous plexus could be roughly estimated by the fractional blood volume obtained by visible light reflective spectrophotometry. The significant decrease of fractional blood volume in the third stage in comparison with the second in normal subjects might represent the fact that blood in the venous plexuses was squeezed out by contraction of the venules. The venous plexuses of the patients with Buerger's disease had a different reaction from those of the normal subjects. The lack of a significant difference between the mean blood volume level in the third and fourth stage in normal subjects might indicate that there were functioning venular valves that prevented venous reflux. The patients with Buerger's disease might have regurgitation owing to incompetent venular valves. Furthermore, the significant difference between the mean fractional blood volume of normal subjects and that of the patients with Buerger's disease in the fifth stage might indicate that there was incompetence of tonus in the venous plexus, together with arteriolar pathology in Buerger's disease.

Dilatation of capillary venules in normal subjects was not observed by IVVMS, while dilatation of capillary venules was observed in patients with arterial occlusive diseases other than Buerger's disease. Thus, dilatation of the capillary venules appears to be due to congestion which results from decreased arterial inflow to the capillary. In patients with Buerger's disease, excessive dilatation and congestion of capillary venules was observed by IVVMS. The congestion resulted from both a decreased arterial blood inflow and dysfunction of the venules. These results obtained by use of the biospectroanalyser and IVVMS show that in Buerger's disease there is an incompetence of tonus in venules and a regurgitation at venular valves. Therefore, Buerger's colour of the hands and feet is probably due to excessive congestion of venous blood in the subpapillary venous plexus, produced by the above mechanisms.

In conclusion, the pathogenesis of chronic ulceration of the hands and feet in patients with Buerger's disease is due not only to a decrease in arterial blood flow, but also to chronic congestion in the subpapillary venous plexus.

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Thallous chloride uptake and DNA profile in parathyroid adenomas

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Thallium isotope scintigraphy is used to localize parathyroid adenomas but the mechanism underlying the technique is poorly understood. While larger adenomas are reliably localized the results are less certain for small tumours. This study explores the relationship between cellular DNA profile and thallium uptake (localization accuracy) in 24 parathyroid adenomas. The DNA profile was assessed using flow cytometry and standard subtraction thallium scintigraphy was performed before surgery. Fifteen of the 24 adenomas demonstrated excessive mitotic activity and 13 of these glands were accurately localized. Of the remaining nine glands, only five were localized accurately ($P < 0.01$, χ^2 *test including Yates' correction). This difference in thallium uptake could not be accounted for on the basis of gland weight. Thallium localization of parathyroid adenomas is related to mitotic activity. This may explain some of the limitations of this technique.*

Keywords: Thallium isotope scintigraphy, flow cytometry, parathyroid, DNA profile

Thallium isotope scintigraphy has been advocated[1–3] to be an effective method of localizing the solitary parathyroid adenoma which will be found in approximately 80 per cent of patients with primary hyperparathyroidism[4]. The accuracy of this investigation varies from centre to centre and its role in the preoperative assessment of patients coming to first neck exploration has been questioned[5,6]. The role of scintigraphy in patients requiring reoperative parathyroid surgery is better established[7]. An accurate localization procedure might improve patient management by reducing operating time and morbidity and perhaps allowing unilateral cervical exploration.

There appears to be poor correlation between tumour activity as indicated by serum calcium or parathyroid hormone concentration and the weight of adenoma. Usually the larger adenomas are more reliably localized than the smaller glands but the degree of thallium uptake is unpredictable. We have described examples of accurate localization of adenomas weighing as little as 200 mg while some glands weighing as much as 12 g were undetected[6]. Flow cytometric studies of mitotic activity in parathyroid adenomas have yielded intriguing results and a characteristic, although poorly understood, finding is that some parathyroid adenomas contain cells with extremely high mitotic rates[8]. Thallium is an analogue of potassium and might be expected to accumulate, on the basis of a quantitative selectivity, in tissues where mitotic activity is increased. *In vitro* studies of normal and transformed thyroid cell lines have shown that malignant transformation is associated with increased mitotic rate and increased thallium uptake[9].

In this prospective study, we have compared the mitotic activity of cells in parathyroid adenomas with the degree of preoperative uptake of thallium by isotope scintigraphy.

Patients and methods

Twenty-four consecutive patients undergoing cervical exploration for primary hyperparathyroidism were studied. In each patient thallium isotope scintigraphy was performed within 9 weeks of surgery. All scans were performed and reported by the same operator (C.B.C.). The information provided by the scans was available to the surgeon (J.R.F.) but did not influence the decision for surgical treatment which was made entirely upon clinical and biochemical grounds.

Surgical strategy was to explore the neck bilaterally, attempting to visualize all four parathyroid glands. In each patient a single adenoma was excised and this was followed by a return to clinical and biochemical normality. All abnormal parathyroid tissue was weighed by the surgeon on a microbalance in the operating theatre and was sent for histological examination with at least one biopsy specimen of a macroscopically normal parathyroid gland for comparison. The operative findings were recorded and compared with the results of the preoperative thallium scintiscan.

A correct localization was defined as a thallium scan which predicted the presence of abnormal parathyroid tissue in a given geographical location. Thus a scan which predicted an adenoma in the lower position was deemed accurate if the operative findings confirmed an abnormally low-lying upper adenoma in a position normally associated with a lower gland. A thallium scan which revealed no evidence of uptake was regarded as an incorrect localization.

The specimens were examined by frozen section and later by paraffin section. Paraffin section tissue was later submitted for flow cytometric analysis.

Patients with secondary hyperparathyroidism or who had undergone previous neck exploration were excluded from this study.

Thallium scan technique

^{201}Thallium, administered as thallous chloride, accumulated in both thyroid and parathyroid tissue and to a lesser extent in surrounding lean tissue. ^{99m}Tc-pertechnetate and later ^{123}I-iodide was used to visualize the thyroid; iodide was preferred since it enabled thyroid images of good quality to be produced consistently.

The night before the scan a 10 MBq dose of ^{123}I was given orally. Anterior imaging was performed with a low energy, general purpose parallel hole collimator attached to a large field of view γ-camera (Siemens, Sunbury-on-Thames, UK ZLC 7500). The data were transferred to a computer (Nodecrest, Byfleet, UK Micas System). The image data were collected in a 128×128 array covering a field of view 19 cm square which included the thyroid and the upper mediastinum. The patient was placed supine on a bed and the head and neck were stabilized with restraining pillows.

Initially a 10 min dual image acquisition was performed in a window centred on the ^{123}I photopeak (159 keV), and in a lower energy window covering the ^{201}Tl photopeaks (69–80 keV). The latter image recorded cross-talk in the ^{201}Tl window from scattered ^{123}I γ-rays. Subsequently, 75 MBq of ^{201}Tl was injected intravenously and a final 10 min image was acquired in the thallium window.

The image processing consisted of a number of steps: (a) the cross-talk image was subtracted from the thallium image; (b) background was removed from the resultant image, followed by a nine-point smooth; (c) a close-fitting region of interest was defined around the smoothed ^{123}I image of the thyroid to ensure that the thallium and iodine images were spatially coincident. If necessary, image shifts were introduced in pixel increments and image magnifications were made the same at both energies to prevent misleading subtraction artefacts. The counts in the region of interest were recorded in both images to normalize the iodine thyroid to the same count total as the thallium thyroid; (d) the normalized iodine image was subtracted from the thallium image. Any increased uptake of ^{201}Tl in parathyroid tissue was then obvious as a high contrast region of activity and, using the defined region of interest and a radioactive marker applied to the suprasternal notch, its position could be reported accurately.

Method for DNA staining of tissues

The normal and adenomatous parathyroid tissues were either stored as archival fixed paraffin embedded blocks (up to 3 months old) or as whole parathyroid glands at −20°C until studied, 30 μm sections were cut from the paraffin embedded blocks and these were deparaffinized in xylene[10].

The sections were then rehydrated at room temperature through a decreasing alcohol concentration and washed twice in distilled water. To obtain cell suspensions, the sections were incubated for 30 min in 1 ml of 1 per cent pepsin in 0·9 per cent NaCl (adjusted to pH 1·5 with 2N HCl). The cells were then washed in 1 ml Isoton (Coulter, Luton, UK) Frozen tissue was thawed, connective and fatty tissue removed using a scalpel and the gland pushed gently through a 100 μm metal sieve using Isoton as suspending medium. Before DNA staining both fixed and frozen cells were filtered through a 30 μm mesh to remove cellular aggregates

All nuclear suspensions were resuspended in 1 ml Isoton and stained by adding 0·25 ml propidium iodide in 4·5 per cent Triton[11]; 1 mg RNase was added for 5 min before DNA measurement. This final step was necessary to prevent contaminating RNA from producing red fluorescence with propidium iodide.

Nuclear DNA content was measured in a Fluorescence Activated Cell Sorter (FACS 420) with a Hewlett Packard (Wokingham, Berkshire, UK) computer for data analysis. Linear amplification was used for DNA fluorescence and an S fit program (Becton Dickinson, Oxford, UK) was used to calculate the percentage of cells in the various phases of the cell cycle. Stained frozen normal lymphocytes and ethanol fixed chicken erythrocytes were used as controls. A total of 5000–15 000 cells per sample were analysed. To eliminate debris from the profile, a live gate of 12 channels was applied to the red fluorescence channel.

Analysis of results

Previous studies[8] have indicated that parathyroid adenomas represent a heterogeneous population with respect to mitotic rates and that some adenomas have abnormally high mitotic rates, without a tendency for these to be normally distributed throughout the group as a whole.

The 24 adenomas were therefore divided into two groups by reference to the 95 per cent confidence limits for the percentage of resting cells (G_0/G_1 phases of the cell cycle) established from a group of 21 histologically normal parathyroid biopsies subjected to flow cytometry as described above.

The 95 per cent confidence limits for the percentage of resting cells in each normal gland were 78–99·7 per cent (mean 88·8 per cent). Adenomas were designated as having excessive mitotic activity if less than 78 per cent of their cells were in G_0 or G_1 phases when analysed by flow cytometry

The relationship of excessive mitotic activity to accurate localization by thallium scintigraphy was then examined statistically using the χ^2 test, employing Yates' correction.

Comparison was also made between gland weight in adenomas with normal and excessive mitotic activity, and positively and negatively localized adenomas.

Results

Of the 24 adenomas, nine displayed normal mitotic activity while 15 had excessive mitotic activity when compared with the percentage of resting cells in 21 normal parathyroid glands (*Figure 1*).

When localization accuracy was examined, six glands were incorrectly localized. Five of these glands were associated with negative thallium scans while the remaining gland, found in the thyrothymic ligament, had been erroneously localized to the right upper position where a normal gland was identified. Eighteen glands were correctly localized. Two of the incorrectly localized glands and 13 of the correctly localized glands had excessive mitotic rates (*Figure 2*).

In total, of 15 adenomas with excessive mitotic activity, 13 (87 per cent) were correctly localized and, of nine with normal mitotic rates, only five (56 per cent) were correctly localized ($P<0·01$, χ^2 test including Yates' correction).

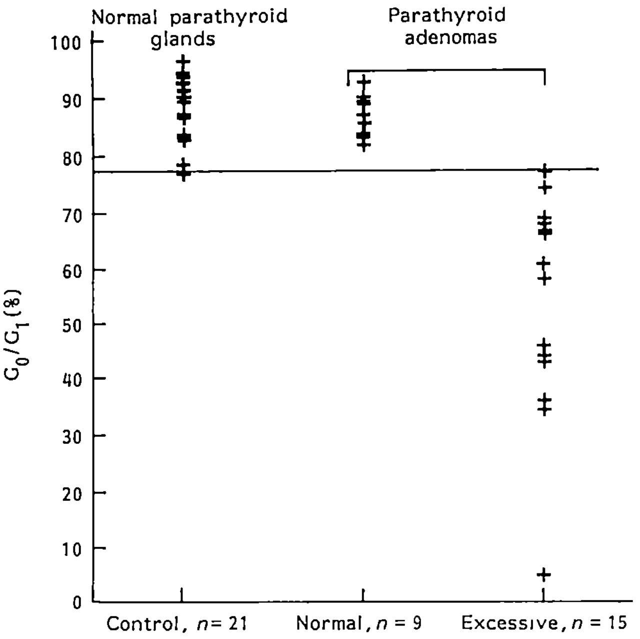

Figure 1 *Graph comparing percentage of cells in resting phases* (G_0/G_1) *of cell cycle in normal parathyroids and parathyroid adenomas.* ——, *95 per cent confidence limit for* G_0/G_1

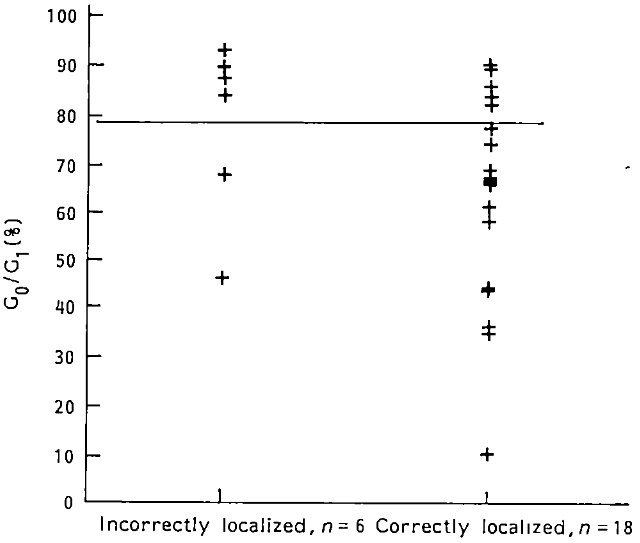

Figure 2 *Graph comparing percentage of cells in resting phases* (G_0/G_1) *of cell cycle in correctly and incorrectly localized parathyroid adenomas* ($P<0·01$, χ^2 *test including Yates' correction*) ——, *95 per cent confidence limit for* G_0/G_1

There was no statistically significant difference in gland weight between glands with normal or excessive mitotic activity or glands which had been correctly or incorrectly localized (*Figure 3*).

Discussion

These results indicate a relationship between an abnormally high mitotic rate in a parathyroid adenoma and the likelihood of that adenoma being accurately localized before surgery by thallium isotope scintigraphy. This finding is not explained by the previously noted relationship between gland weight and localization accuracy.

The mechanism of thallium localization is uncertain[12]. Thallium is an analogue of potassium and as such might be expected to accumulate in actively dividing tissues along with the expanding cytosol mass. Mechanisms of thallium uptake are ouabain-sensitive[13], with thallium uptake being mediated, at least in part, by sodium–potassium ATPase, and the

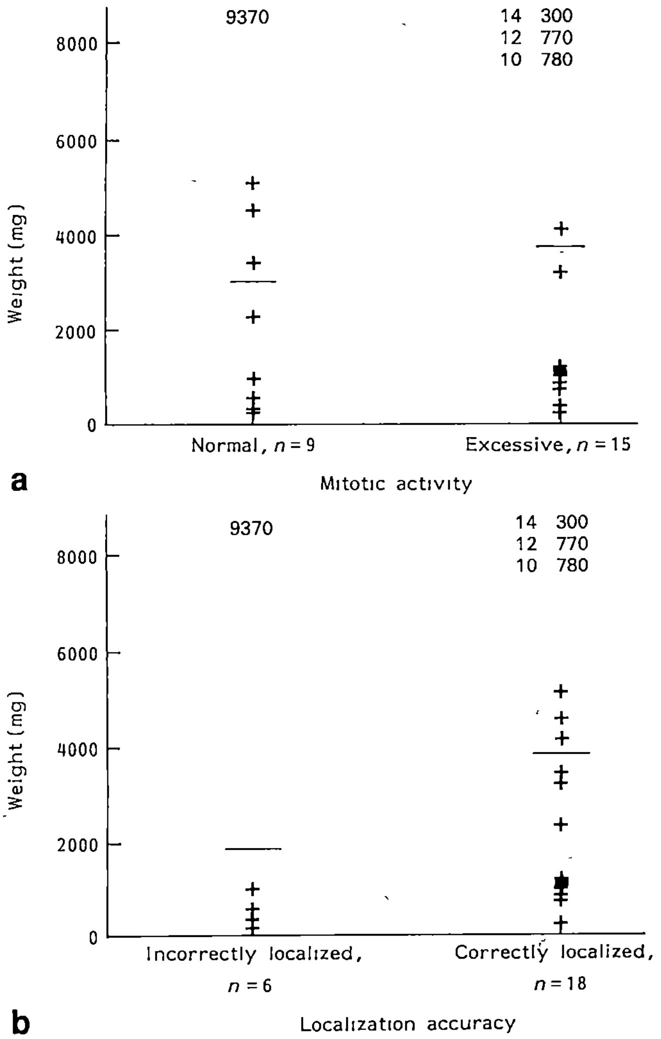

Figure 3 *Graph comparing gland weight with* **a** *mitotic activity and* **b** *localization accuracy for correctly and incorrectly localized parathyroid adenomas. No statistically significant differences*

potassium being replaced by thallium[14]. This is also supported by the analogous distribution of thallium and potassium[14]

Recent studies of malignant tumours have shown that thallium accumulates rapidly *in vitro*[15,16], and thallium localization has been described in cerebral metastases[17], bronchial carcinoma[18] and carcinoma of the thyroid[19,20]. False positive localization of a parathyroid adenoma due to mediastinal Hodgkin's disease has been reported[21].

Increases in mitotic rate which are associated with malignant transformation are also associated *in vitro* with increased thallium uptake[9]. Since thallium localization is dependent upon uptake, our results suggest that *in vivo* the phenomenon of thallium localization of a parathyroid adenoma is at least partially explicable on the basis of increased mitotic rate This may explain the unpredictability of thallium isotope scintigraphy. Although, in general, localization accuracy is related to gland weight, those smaller adenomas with high mitotic rates would take up large amounts of thallium and be localized accurately. Certain larger tumours, which should be within the resolution of thallium scan, remain undetected because of lower mitotic rates and correspondingly lower thallium uptake.

Better understanding of the biochemical and physiological processes involved in neoplastic transformation of the parathyroid glands may lead to refined and more sensitive localization modalities.

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Duodenogastric reflux and gastric histology after cholecystectomy with or without sphincteroplasty

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Sixteen patients who had undergone cholecystectomy plus sphincteroplasty, 14 cholecystectomized patients and ten control patients were studied to evaluate whether differences existed in duodenogastric reflux and whether these were related to morphological damage of the gastric mucosa. Duodenogastric bile reflux during fasting was evaluated by measuring the concentration of total bile acids (by an enzymatic method) and single bile acids in the gastric juice by high performance liquid chromatography. The damage was evaluated histologically by systematic endoscopic biopsy of the antrum and body of the stomach. There was a statistically significant difference in fasting bile reflux between the three groups (Kruskal–Wallis test, $P<0{\cdot}001$*), and the group that underwent cholecystectomy plus sphincteroplasty had a significantly higher median value than the cholecystectomized group (*$P<0{\cdot}05$*) and the control group (*$P<0{\cdot}01$*). The distribution of chronic antral atrophic and superficial gastritis was different in the three groups (*χ^2 *test,* $P<0{\cdot}005$*). Chronic atrophic gastritis was associated with cholecystectomy plus sphincteroplasty (*$P<0{\cdot}01$*), while chronic superficial gastritis was more frequent in cholecystectomized patients. These results suggest that there may be more duodenogastric reflux after cholecystectomy plus sphincteroplasty than after cholecystectomy alone, and that there may be a correlation between the amount of duodenogastric reflux and the severity of mucosal damage.*

Keywords: Duodenogastric reflux, cholecystectomy, sphincteroplasty

Pathological duodenogastric reflux may occur following operations that damage, remove or bypass the pyloric sphincter, or even when the stomach is intact[1–3] When the stomach is intact, duodenogastric reflux has been associated with various diseases, such as cholelithiasis, gastric ulcer and chronic pancreatitis[2], and has been considered as a consequence of cholecystectomy[4–8]. Duodenogastric reflux has been associated with gastric mucosal damage, and this may occur after cholecystectomy[9–11]

It is known that the sphincter of Oddi is the main regulator of the bile flow into the duodenum[12] but it is not known what effect the loss of its function has upon duodenogastric reflux.

The aims of the present study were: (a) to evaluate whether more duodenogastric reflux is found after cholecystectomy plus sphincteroplasty than after cholecystectomy alone; (b) to determine whether sphincteroplasty is associated with a qualitative difference in bile acid reflux into the stomach of cholecystectomized patients; and (c) to establish whether there is any association between the two types of operation and gastric mucosal damage

Patients and methods

Three groups of patients were studied Group 1 consisted of 16 patients who had undergone cholecystectomy plus sphincteroplasty for gallstones and common bile duct stones (ten women, six men, mean age 55 years, range 31–78 years) It is our routine policy to perform a sphincteroplasty when common bile duct stones are encountered[13]. The sphincter section is approximately 12–15 mm long Duodenogastric reflux was evaluated after a mean period of 44 months from surgery (range 17–86 months)

Group 2 consisted of 14 patients who had undergone cholecystectomy for gallstones, in whom preoperative cholangiography had excluded lesions of the main bile duct (eight women, six men, mean age 51 years; range 34–78 years) Duodenogastric reflux was evaluated after a mean period of 36 months from surgery (range 12–74 months)

Group 3 consisted of ten patients about to undergo surgery for repair of an inguinal or femoral hernia in whom upper abdominal ultrasonography and oesophagogastroduodenoscopy had excluded biliary and gastroduodenal lesions These patients made up the control group.

There were no significant differences between the groups in terms of age and sex and, with regard to groups 1 and 2, in terms of the time lapsed since operation

All subjects gave their informed consent to the study

Duodenogastric reflux was assessed after a 12-h fast by aspiration of gastric contents every 15 min for 1 h by means of a nasogastric tube positioned on the greater curvature of the stomach under fluoroscopic control. The concentration of total intragastric bile acids was measured by an enzymatic method (Enzabile®, Nyegaard and Company, Oslo, Norway) Single bile acids were separated by high performance liquid chromatography according to the method of Schindlbeck *et al*[14] For group 3 we were unable to separate the single bile acids because of the small reflux volume and low concentration of total bile acids The coefficient of variation for the chromatographic measurement of single bile acids was always less than 6 per cent To calculate the bile flow, the concentration of total and single bile acids in each of the four samples of gastric juice was multiplied by the volume of the sample The entire quantity of total and single bile acid reflux in 1 h was calculated by the summation of the flow values of the four 15-min samples and expressed as 'fasting bile reflux' in μmol/h (Reference 15)

To evaluate gastric mucosal damage, all the patients (except one in group 1 who refused the procedure) underwent oesophagogastroduodenoscopy During this examination, two biopsies were taken from the antrum and two from the body of the stomach Biopsy specimens were fixed in buffered formalin, embedded in paraffin, cut into sections with a microtome (5 μm thickness) and stained with haematoxylin and eosin, Van Gieson's solution, periodic acid-Schiff (PAS) and Alcian–PAS Histological damage was graded according to the gastritis classification of Morson and Dawson[16] All the histopathological specimens were

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read at a single sitting by one pathologist (M.L.C.) who did not know to which group they pertained.

Statistical analysis was performed with the Kruskal–Wallis test for non-parametric one-way analysis of variance[17] and the χ^2 test for the analysis of contingency tables[18]

Results

The distribution of the fasting bile reflux values for total bile acids in the three groups of patients is shown in *Figure 1*. After cholecystectomy plus sphincteroplasty, the median value of fasting bile reflux was 65·5 μmol/h (range 2·6–506·6 μmol/h), higher than that found after cholecystectomy alone (13 μmol/h; range 0·06–95·5 μmol/h) and in the control group (1·6 μmol/h; range 0·8–12·8 μmol/h). These differences in fasting bile reflux between the three groups were statistically significant (Kruskal-Wallis test, $P<0{\cdot}001$). After multiple comparisons within the analysis of variance, fasting bile reflux after cholecystectomy plus sphincteroplasty was found to be significantly greater than either after cholecystectomy alone ($P<0{\cdot}05$) or in the control group ($P<0{\cdot}01$), while the difference between fasting bile reflux after cholecystectomy and in the control group was not statistically significant ($P>0{\cdot}05$). After examining the reflux of single bile acids in each study group, it was found that in group 1 the proportion of secondary bile acids in the refluxate was greater than that of group 2 (*Table 1*).

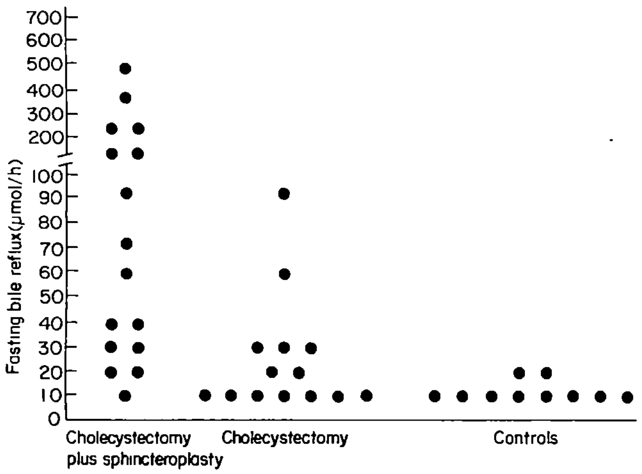

Figure 1 *Distribution of fasting bile reflux values in 16 patients following cholecystectomy plus sphincteroplasty, in 14 patients following cholecystectomy and in ten control patients*

Data referring to the histology of the gastric mucosa of the three groups of patients are reported in *Table 2*. The frequency distribution of antral histological findings was different in the three groups (χ^2 test, $P<0{\cdot}005$). The frequency of chronic antral atrophic gastritis was higher in group 1 than in the control group (χ^2 partitioning, $P<0{\cdot}01$), and the same was true for chronic superficial gastritis in group 2. As far as the body of the stomach was concerned, similar differences were found but they were less evident. Finally, both chronic atrophic gastritis in group 1 and chronic superficial gastritis in group 2 were more frequent in the antrum than in the body.

Discussion

This study shows that after cholecystectomy plus sphincteroplasty there is more duodenogastric reflux than after cholecystectomy alone or in subjects with intact gallbladders. These differences were statistically significant.

The most commonly accepted explanation for increased duodenogastric reflux after cholecystectomy is that the loss of the bile reservoir function leads to a continual flow of bile into the duodenum. Consequently bile is also present in the duodenum during the fasting state when episodes of physiological duodenogastric reflux can be observed[4,6,7,10,11]. However, this theory has not been substantiated; on the contrary it is known that the main regulator of bile flow into the duodenum is the sphincter of Oddi[12] and that even after cholecystectomy a rhythmic flow of bile into the duodenum remains, a flow that can be related to the rhythm of interdigestive motor complexes[19]. Therefore, we consider that surgical elimination of the function of the sphincter of Oddi is the real cause of continual bile flow into the duodenum, and that this might allow more duodenogastric reflux than after cholecystectomy because of the passage of a greater amount of bile into the duodenum and thence into the stomach during physiological duodenogastric reflux.

In the patients who underwent cholecystectomy plus

Table 1 *Fasting bile reflux (FBR) of single bile acids in 16 patients after cholecystectomy plus sphincteroplasty and in 14 patients after cholecystectomy*

	Cholecystectomy plus sphincteroplasty		Cholecystectomy	
	Median FBR (μmol/h)	%	Median FBR (μmol/h)	%
Primary bile acids	46·1 (20·8–116·1)	74	10·0 (3·98–19·97)	79
Cholic acid	22·9 (9·6–50·6)	39	5·0 (1·87–9·80)	38
Chenodeoxycholic acid	20·1 (12·6–49·7)	35	6·0 (2·11–10·34)	46
Secondary bile acids	16·25 (7·6–30·6)	26	2·68 (0·99–3·71)	21
Deoxycholic acid	14·3 (6·2–28·4)	25	2·1 (0·99–3·58)	16
Lithocholic acid	0·95 (0·8–6·5)	2	0·0 (0·05–1·28)	0

Values in parentheses are interquartile ranges

Table 2 *Gastric mucosal histology in 15 patients after cholecystectomy plus sphincteroplasty, in 14 patients after cholecystectomy and in ten control patients*

	Cholecystectomy plus sphincteroplasty		Cholecystectomy		Control group	
Histology	Antrum	Body	Antrum	Body	Antrum	Body
Normal	3 (20)	8 (53)	5 (36)	10 (71)	5 (50)	8 (80)
Chronic superficial gastritis	5 (33)	4 (27)	9 (64)	4 (29)	5 (50)	2 (20)
Chronic atrophic gastritis	7 (47)	3 (20)	0 —	0 —	0 —	0 —

Values in parentheses are percentages

sphincteroplasty, we found a higher relative amount of secondary bile acids in the refluxate than in the group of patients who underwent cholecystectomy alone. These data could support the contention that there is a more continuous flow of bile into the intestine after sphincteroplasty than after cholecystectomy alone. This continual bile flow in the small intestine could consequently cause a more rapid passage of bile acids into the colon and a prolonged exposure of primary bile acids to the colonic bacterial flora with a consequent increase in the production of secondary bile acids[20,21].

Finally, our results show a significant association between cholecystectomy plus sphincteroplasty and chronic atrophic gastritis of the antrum, and a greater frequency of chronic antral superficial gastritis in patients having cholecystectomy alone. We believe that these results are valid, notwithstanding the fact that the number of patients in each subgroup of *Table 2* was small, because the differences were so striking. These findings suggest that there may be a correlation between the amount of duodenogastric reflux and the severity of mucosal damage. This hypothesis is also supported by the fact that both chronic atrophic gastritis and chronic superficial gastritis were more frequent in the antrum, an area closer to the source of the reflux than the body of the stomach.

The effects of duodenogastric reflux on the gastric mucosa are controversial. Some authors have reported an association between cholecystectomy and chronic gastritis[9,10] while others have failed to demonstrate any such association[22]. The duodenogastric reflux found after gastric surgery, however, especially after Billroth II gastric resection, has been associated with more serious lesions of the mucosa of the stump, ranging from chronic atrophic gastritis to intestinal metaplasia and cancer[23–26].

The results of our study indicate that gastric mucosal damage may follow cholecystectomy plus sphincteroplasty in association with bile reflux. Therefore, we propose that three postsurgical conditions, namely postcholecystectomy, post-cholecystectomy plus sphincteroplasty, and postgastric resection, are characterized by a progressively greater degree of duodenogastric reflux corresponding to progressively greater damage of the gastric mucosa. This does, of course, raise the possibility and concern that these changes might proceed further to intestinal metaplasia and even to malignant change[27,28].

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Abstracts of papers presented at the Tenth Meeting of the British Association of Endocrine Surgeons, The London Hospital, Whitechapel, 24 May 1990

Goitre in childhood and adolescence

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Because of the rarity of goitre presentation in childhood and adolescence (0–16 years), especially carcinoma[1], there are difficulties in formulating a plan of management. An unusual papillary thyroid carcinoma in an 8-year-old boy has prompted a review of surgical goitres at the Bristol Children's Hospital.

A 23-year period, from 1967–1989 inclusive, was examined from retrospective data deriving from operating theatre and histopathology records All available histological and cytological material has been reviewed in addition The hospital serves a total population of ≈400 000 and functions as an Oncology Referral Centre

As anticipated, the yield was small: only 14 surgically treated goitres were forthcoming The case distribution was· nodular goitre (including cystic change), 7, primary thyrotoxicosis, 1, Pendred's syndrome hyperplastic goitre, 1; papillary carcinoma, 1. From this small series, significant clinical, operative or pathological difficulty was experienced in six cases

The following tentative conclusions can be made The wider use of fine needle aspiration biopsy cytology, under a short anaesthetic if necessary, could assist the diagnosis There is a need for a greater recognition of the existence and significance of lymphocytic thyroiditis in this age group[2] Peroperative frozen section diagnosis is valuable in neoplastic cases to 'tailor' the surgery

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Management of isolated thyroid swellings using fine needle aspiration cytology – a prospective six year study

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Fine needle aspiration cytology (FNAC) has become increasingly regarded as the diagnostic method of choice in thyroid swellings In a six-year prospective study the accuracy of FNAC in the diagnosis of isolated thyroid swellings (ITS), and the resulting impact on the frequency of operation, was assessed. Three hundred and seven (78 per cent) of 395 patients presenting with an ITS underwent surgical excision The positive predictive value of 'malignant' cytology was 100 per cent but only 53 (83 per cent) of 64 malignant ITS with satisfactory aspirates were identified cytologically as either 'malignant' (33 per cent) or 'possibly neoplastic' (50 per cent) FNAC was unsatisfactory in two (3 per cent) of malignant ITS and 11 (17 per cent) were falsely classified as non-neoplastic. Satisfactory aspirates were obtained in 91 per cent of 181 removed neoplastic lesions (including follicular adenomas). Of these 76 per cent were correctly identified by FNAC as 'possibly neoplastic' or 'malignant' and 24 per cent were false negatives. The overall accuracy for removed ITS was low at 69 per cent The reduction in the frequency of operation for ITS since the introduction of FNAC was 21 per cent and we continue to remove 75 per cent

Review of the literature on FNAC in thyroid swellings showed many variations in the method of calculating accuracy Recalculation according to strict criteria showed that the accuracy of FNAC in thyroid swellings is less than has been widely accepted.

Riedel's thyroiditis: an extinct disease or lymphoma in disguise?

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Riedel's struma or invasive fibrous thyroiditis is a rare chronic inflammatory disease involving the thyroid gland and surrounding soft tissue, which was first recognized by Bernhard Riedel in 1893 and described in published reports in 1896 and 1897 Although always included in classifications of thyroiditis, only 143 cases had been reported in the entire English literature up to 1960. Furthermore, during the past 30 years, only an additional 42 cases have been identified.

During the past three decades no patients were seen at the University of Michigan in whom primary diagnosis of Riedel's was made despite an active thyroid service. However, two patients were referred after an initial clinical and pathologic diagnosis had been established elsewhere

The first case was a 32-year-old female initially treated by isthmusectomy and tracheostomy but recurrence of airway compression within two months led to her referral in 1979. After a bilateral partial thyroidectomy and new tracheostomy, histopathologic and immunohistochemical study resulted in a new diagnosis of malignant lymphoreticular neoplasm After staging, she was treated with external radiation therapy with complete resolution of the disease in her neck

The second case was a 33-year-old female who developed a firm diffuse lesion in the thyroid which rapidly enlarged despite thyroid suppression therapy. An isthmusectomy was performed, which has relieved tracheal compession Pathologic studies were consistent with Riedel's and she is currently being treated with steroids. Immunohistochemical studies will be reported.

It is concluded that a diagnosis of Riedel's should be accepted only after detailed immunohistochemical study

Parathyroid risk in thyroid surgery: a plea against early postoperative prescription of vitamin D

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Seven hundred and twenty-nine consecutive patients underwent thyroidectomy in 1988 in the same institution, including 477 (68 per cent) bilateral resections and 242 (33 per cent) total thyroidectomies An effort was made to see and save all four parathyroids and their blood supply. Early postoperative hypoparathyroidism was defined at day five, by serum calcium <8 mg/dl and serum phosphate >4 mg/dl, or by serum calcium only if <7·5 mg/dl. Patients afflicted with early hypoparathyroidism were given calcium tablets without any vitamin D for one year at most Follow-up, checking serum Ca, P and i PTH was done on a three month basis during one year. Permanent hypoparathyroidism was defined by persistence of the above mentioned criteria after one year when vitamin D was started.

Twenty-seven patients (5·67 per cent out of 477 bilateral thyroid resections) experienced early postoperative hypoparathyroidism. Inciting factors were previous thyroid surgery (4), radio-iodine treatment (2); modified neck dissection (2), sternal split with mediastinal node clearance (1), visualization of one parathyroid gland only (three redo cases) and autotransplantation of more than one parathyroid (one case)

One patient was lost for follow-up Twenty-five others recovered a normal parathyroid function One is permanently hypoparathyroid (one redo case with other risk factors)

Painstaking parathyroid dissection produces no permanent hypoparathyroidism after primary surgery, if vitamin D is not given in the early postoperative period We suggest that avoidance of early vitamin D prescription in cases of early postoperative hypoparathyroidism, leading to mild sustained hypocalcaemia, stimulates the spared parathyroid glands (including a possible fifth) and therefore allows full recovery of the parathyroid function

Weight change after treating thyrotoxicosis (a comparison of therapies) and hypothyroidism

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Little has been published on the effect on body-weight of treating thyroid dysfunction. We performed a retrospective study of 65 patients, randomly selected, treated by three treatment regimes (surgery, medical therapy and radio-iodine), and of 25 patients treated for primary hypothyroidism In one year after partial thyroidectomy, 20 patients gained a mean of 6·3 kg (95 per cent confidence interval (c.i.) 4 to 9·2 kg), 21 patients treated with carbimazole gained a mean 5·4 kg (95 per cent c.i 5·2 to 9·6 kg), $P<0{\cdot}001$ in all three groups The weight change did not significantly differ between the three groups. In all three groups 54–67 per cent of the weight gain occurred in the first three months. The patients treated for hypothyroidism lost a mean of only 0·6 kg body weight (95 per cent c.i. −2·2 to +1·1 kg), $P>0{\cdot}1$ in the 12 months after instituting therapy.

These data suggest that all patients treated for thyrotoxicosis will gain weight in the 12 months after the onset of therapy and that the weight gain is the same, irrespective of the therapy used. Patients with hypothyroidism will not tend to lose weight after instituting thyroxine replacement. All patients with thyroid dysfunction would benefit from dietary advice at the onset of therapy.

Flow volume loops in goitres

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Plain radiology is the standard method of assessing tracheal compression in patients with goitres However this test does not provide information on the air flow changes present in the upper respiratory tract. Flow volume loops are a simple, quantitative assessment of the degree of upper airway obstruction in both the inspiratory and expiratory phases of the respiratory cycle. This study investigates the effect of thyroidectomy on flow volume loop curves in 51 patients. Flow volume loops were performed preoperatively and at a mean of 18 weeks postoperatively The histology and weight of gland excised was recorded. The vocal cords of all patients were normal postoperatively

There was a significant increase in postoperative variables in the flow volume loops The improvement in respiratory function was maximal in the inspiratory phase of the flow volume loop

	Preop	Postop	*P* value
Max inspiratory flow rate (l/s)	3·9+0·2	4·9+0·2	<0·001
Inspiratory $V_{\max}$ 50 (l)	3·7+0·2	4·7+0·2	<0·001
Max expiratory flow rate (l/s)	5·4+0·3	6·3+0·3	<0·001
Expiratory $V_{\max}$ 50 (l)	3·8+0·2	4·1+0·2	<0·01

Values are mean+s.e.m., paired *t*-test

There was no significant correlation however, between any of these variables and the weight of the gland removed

In conclusion, this study demonstrates a significant increase in airflow in patients post-thyroidectomy, especially on inspiration, but the degree of improvement is not related to the weight of the gland

Intra-operative radionuclear *meta*-iodobenzylguanidine scanning of pheochromocytomas: a pilot study

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Increased awareness about multicentricity and recurrence or metastasis of pheochromocytomas, possibly overlooked by pre-operative localization methods, prompted us to develop a technique to assess the feasibility of intra-operative radionuclear detection of pheochromocytomas or their metastases.

A small (12 cm) probe with a cadmium-telluride detector has been manufactured. Eleven patients entered the study· five with seemingly sporadic unilateral pheochromocytomas, one with bone metastases from a previously resected pheochromocytoma, and five controls ('incidentalomas' or aldosteronomas). Each received (one month after pre-operative scan with *meta*-iodobenzylguanidine, MIBG) thyroid blockade six days pre-operatively and an i.v. injection of 500 μCi of ^{125}I-labelled MIBG, three days pre-operatively. Intra-operatively adrenals and intra-abdominal organs were scanned. Blood specimens were countered.

Three patients had a positive pre-operative MIBG scan and in one other a scan was not done. Specimens ranged from 8·5 to 225 g All had positive intra-operative scanning with a count ratio pheochromocytoma/liver from 14/2 to 65/2·5 and pheochromocytoma/normal adrenal of 60/2. One patient had a negative pre-operative MIBG scan with a 30 g specimen and demonstrated no intra-operative uptake One patient with bone metastases and a negative pre-operative MIBG scan demonstrated a positive intra-operative uptake with a ratio bone metastasis/normal bone of 10/0·5. All five control patients demonstrated a negative uptake. In positive cases the percentage uptake of the i.v. injected dose ranged between 0·02 and 9 per cent, ratios 1 g tumour/1 ml blood reached 666, and 1 g tumour/normal tissue reached 100.

It is concluded that intra-operative MIBG scanning of pheochromocytomas is possible and might detect deposits overlooked by pre-operative MIBG scans

Large adrenal mass in the era of adrenal imaging: benign or malignant

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The differential diagnosis and optimal management of adrenal masses remains a matter of controversy. Adrenal cortical tumours producing syndromes of steroid hormone excess have an estimated incidence of approximately four per million per year, equally divided between adenomas and carcinomas. Pheochromocytomas occur with an estimated incidence of 1·5 per million per year with only 10–20 per cent being malignant Reviews of both functioning and 'incidental' adrenal masses have emphasized the positive correlation between size and the likelihood of malignancy Recommended thresholds for surgical exploration have included diameters of 3–3·5, 5 and 6 cm. In this study, we have examined the clinical, radiological, scintigraphic 6-β-[^{131}I]iodomethyl-19-norcholesterol or meta-[^{131}I]iodobenzylguanidine) and pathologic characteristics of large adrenal masses (>5 cm in diameter), both hyperfunctioning and non-hyperfunctioning seen at the University of Michigan between 1977 and 1988. Twenty-nine of 468 patients having NP-59 scans and 16 of 52 having MIBG scans for possible sporadic intra-adrenal pheochromocytoma met these criteria Adrenal cortical and/or medullary function was evaluated in all cases. Forty-three of the 45 patients also had CT scans and more recent cases had MRI studies. In all but three cases, a tissue diagnosis was made by operation, fine needle biopsy or at autopsy

Only 15 masses proved to be malignant primary adrenal cortical carcinoma in seven, adrenal metastases in 5 and adrenal lymphoma in 3 All 6 patients with bilateral masses proved to have metastatic disease or lymphoma Of the 30 patients with benign masses, 16 were pheochromocytomas and 6 were benign cortical adenomas. Additional diagnoses included myelolipomas (2), ganglioneuroma, adrenal haematoma and adrenal cyst (4)

Functional scintigraphy with NP-59 for suspected cortical lesions and MIBG for suspected pheochromocytomas most frequently provided insight into the nature of the large adrenal lesion. With few exceptions, neither CT nor MRI were capable of differentiating benign from malignant masses or identifying the specific nature of the mass

Multiple endocrine neoplasia type 2a: the investigation and management of a family on two continents

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Investigation following discovery of an index patient with medullary thyroid carcinoma and pheochromocytoma[1] has, over the past several years, resulted in the indentification of a Northern Ireland multiple endocine neoplasia type 2A (MEN 2A) family, some of whom had earlier emigrated to Australia. Three generations of the family have now been screened by a combination of clinical examination, biochemical assessment and, where appropriate, radiological investigation

Of seven siblings in the first generation, six (including the index patient) have proven medullary thyroid carcinoma and two have pheochromocytoma, suggesting a high degree of penetrance of the gene. Four of these patients have died from their disease In addition, 7 of 15 individuals comprising the second generation have now undergone surgery for medullary carcinoma and pheochromocytoma (3) Screening of the children of the third generation by clinical examination and estimation of plasma calcitonin values is ongoing.

Currently we are screening family members with the gene probes TBQ 14.34, MCK 2 and RBP 3, which are flanking markers for what is thought to be the MEN 2A locus on chromosome 10. The significant part played by serendipity and the chance meeting of surgical colleagues in the elucidation of this family will be related.

1. Russell CFJ. Medullary carcinoma of the thyroid gland *Ulster Med J* 1980; **49**. 54–64.

Improvement of hand strength after correction of hypercalcemia in primary hyperparathyroidism

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Fatigue and muscular weakness are common symptoms in primary hyperparathyroidism (HPT). Many patients experience clinical improvement postoperatively During the last decade studies have been published where this improvement has been objectively demonstrated[1,2]. In this study, further evidence is presented that patients, undergoing successful parathyroidectomy due to primary HPT, improve their muscle force postoperatively.

Ten patients with HPT and seven patients with benign thyroid lesion were studied. All patients with hypercalcaemia had excision of a parathyroid adenoma and all patients in the control material had a hemithyroidectomy performed The patients were studied by means of a computer-based program (HASTRAS = hand strength analysis system) Maximal instant grip power as well as grip power during a 30 s period, maximal pronation and supination were studied.

Patients with HPT had a depressed muscle strength compared to the control group The maximal grip power increased in the HPT group ($P<0{\cdot}01$) but was unchanged in the control group Both pronation and supination power also increased in the HPT group ($P<0{\cdot}001$, $P<0{\cdot}02$) but was unchanged among the controls.

These results confirm previous findings that hypercalcaemia often produces muscle weakness and that parathyroidectomy improves muscle force. We think a liberal attitude towards surgery in HPT is recommended.

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2. Kristoffersson A, Bjerle P, Stjernberg N, Jarhult J Pre and postoperative respiratory muscle strength in primary hyperparathyroidism. *Acta Chir Scand* 1988, **154**: 415–18

Effect of parathyroidectomy on muscle hypertonicity associated with primary hyperparathyroidism

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Disorders of calcium metabolism can be associated with abnormalities of muscle function One symptom of primary hyperparathyroidism is muscle weakness. Muscle tone has been measured before and after removal of a parathyroid adenoma in seven patients (two male, five female, age range 53–76 years) using a computerized version of the Wartenberg pendulum test[1] This system can accurately measure small changes in muscle tone which is denoted by the relaxation index calculated by the computer (normal range = 1·54 + 0·09), a low index indicates hypertonicity and a high index flaccidity[1]

All patients had a fall in corrected serum calcium associated with surgery (mean + s.e.m pre-operative = 2·71 + 0·05 mmol/l^{-1}, post-operative = 2·28 + 0·04 mmol/l^{-1}) All patients had a corresponding increase in the relaxation index (mean + s.e m. pre-operative = 1·43 + 0·07, postoperative 1·69 + 0·05)

Three patients pre-operatively had evidence of marked muscle hypertonicity and these patients had the greatest benefit from surgery. It was noted that there was a definite relationship between calcium and muscle tone with strong inverse linear correlation between the corrected serum calcium and the relaxation index ($R = -0{\cdot}863$, $P<0{\cdot}0001$).

The data show that muscle weakness resulting from primary hyperparathyroidism can be associated with increased tone of the muscle and the hypertonicity can be corrected by surgery

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Cardiac output in asymptomatic primary hyperparathyroidism: stigmata of early cardiovascular dysfunction?

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Recent studies[1,2] have suggested that there may be an increased incidence of cardiovascular disease in patients with primary hyperparathyroidism and that this trend may be reversed by parathyroidectomy. The ultimate measure of cardiovascular function is cardiac output; this may be accurately, conveniently and safely calculated by Doppler echocardiology.

The present study comprised ten normotensive patients with asymptomatic primary hyperparathyroidism. All had an elevated serum calcium (mean 3·1 mmol/l^{-1}, range 2·9–3·2) and normal renal function (mean serum creatinine 96 μmol l^{-1}; range 78–114). All ten patients underwent a successful parathyroidectomy with excision of a solitary adenoma. In all patients the resting cardiac output was measured by Doppler echocardiography before and within one month following surgery. Five patients with non-toxic goitre undergoing thyroidectomy were studied as controls.

The mean cardiac output of the patients with hyperparathyroidism was 7·2 l min^{-1} (range 5·3–8·9) before surgery and 6·3 l min^{-1} (range 4·9–7·8) after return of the serum calcium to normal. The control patients had a mean cardiac output of 5·8 l min^{-1} (range 5·2–6·3).

In eight of ten patients there was fall (mean 1·2 l min^{-1}; range 0·4–3·5) in the cardiac output following parathyroidectomy; there was no difference in the heart rate, implying a change in the stoke volume Although these results should not be taken as a definite indication for surgery, they suggest that there may be an alteration in cardiovascular function in mild hypercalcaemia. Further studies are required to determine whether these observations are of clinical importance in the long-term follow-up of patients with asymptomatic primary hyperparathyroidism.

1 Palmer M, Adami H-O, Bergstrom R *et al* Mortality after surgery for primary hyperparathyroidism: a follow-up of 44 patients operated on from 1956 to 1979. *Surgery* 1987, **102**: 1–7.

2 Palmer M, Bergstrom R, Akerstrom G *et al.* Survival and renal function in untreated hypercalcemia. *Lancet* 1987, **i**: 59–62.

Effect of subtraction scanning localization of parathyroid tumours on operating time

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Accurate pre-operative localization of abnormal parathyroid glands may result in a reduction in operating time for parathyroidectomy. We analysed the duration of surgery in a consecutive series of 81 patients undergoing parathyroidectomy by a standard neck exploration, with a view to identifying at least four parathyroid glands in each patient. Sixty-five patients underwent pre-operative localization by thallium-201 and technetium-99^{m} subtraction scanning. The remaining 16 patients had hyperparathyroidism secondary to renal disease, where the technique is not useful in identifying hyperplastic parathyroid glands.

Of the 48 parathyroid tumours found at operation, 31 were accurately localized by the scan, and these patients had a median operating time of 90 min. When the tumour had not been localized pre-operatively, the median time was similar (80 min).

Of the 33 patients with parathyroid hyperplasia, 16 were not scanned, 3 were accurately localized and in the remaining 14 the scan was unhelpful. The median operating time for patients scanned pre-operatively was similar to patients not scanned, 105 and 110 min respectively. The median (and range) operating time for the total series was 95 (40–170) min The median operating time for removal of a parathyroid tumour of 85 (40–135) min was shorter than that for the hyperplasia group, 110 (50–170) min ($Z=2{\cdot}95$, $P<0{\cdot}002$)

We conclude correct pre-operative localization of parathyroid tumours does not reduce operating time, and that operating time for parathyroidectomy may be expected to be shorter when operating for tumour than for hyperplasia.

Parathyroid surgery under loco-regional anaesthesia

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Most patients with hyperparathyroidism (HPT) are fit for general anaesthesia. We report our surgical experience using a local anaesthetic technique in six women and one man (aged 66–91 years) with symptomatic primary HPT (serum calcium: 2·63–3·2 mmol/l^{-1}) in whom general anaesthesia was contraindicated due to severe pre-existing disease (cardiorespiratory 4 patients, neurological 2 patients, cerebrovascular 1 patient).

Bilateral modified superficial cervical plexus block (0·5 per cent prilocaine with 1/200 000 adrenaline) and mild intravenous sedation allowed a standard cervical exploration to be performed. In six patients a solitary adenoma (weight 76 mg–3·5 g) was removed from the neck. Multiglandular disease in one patient required transcervical thymectomy and subtotal parathryoidectomy. All patients became normocalcaemic after surgery. One patient died of a cerebrovascular accident 2·5 weeks postoperatively. Another suffered a severe exacerbation of pre-existing Parkinson's disease.

In appropriate cases curative parathyroid surgery may be performed using local anaesthesia when there are major contraindications to general anaesthesia, but there is still a substantial risk of morbidity/mortality from concomitant medical disease.

Clinicopathologic peculiarities in parathyroid disease presenting with hypercalcaemic crisis

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To illustrate factors of importance in the management of hypercalcaemic crisis in primary hyperparathyroidism, we have studied a large series of such patients treated at the University of Michigan.

The study comprised 56 patients (39 women and 17 men) with serum calcium exceeding 3·5 mmol/l^{-1} (14 mg/100 ml) and symptoms of calcium intoxication All surgical specimens were re-examined, and the parathyroid pathology was classified as adenoma in 45 cases, hyperplasia in nine cases and carcinoma in 2 cases.

From our findings we conclude the following. Compared to primary hyperparathyroidism in general, hypercalcaemic crisis is associated with an over-representation of young patients (20 per cent were under 40 years of age). Oxyphilic parathyroid adenomas may be functioning to a degree causing hypercalcaemic crisis (illustrated by 4 cases). In hypercalcaemic crisis, mitotic activity is common in parathyroid lesions (hyperplastic glands as well as adenomas) without any evidence of malignancy such as invasive growth or recurrence. The size of most parathyroid adenomas causing hypercalcaemic crisis (median 2·5 cm) permits diagnosis by imaging techniques, but the correlation between the size of an adenoma and the degree of hypercalcaemia is poor.

Relationship between allele losses and parathyroid pathology in sporadic and familial hyperparathyroidism

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Molecular techniques offer possibilities to study hereditary tumours, such as those associated with the autosomal dominant multiple endocrine neoplasia type-1 (MEN-1) syndrome. The gene for MEN-1 has been mapped to chromosome 11. Tumour and normal tissue genotypes were compared in 27 cases of hyperparathyroidism for loci on chromosome 11 and eight other chromosomes Allele losses for chromosome 11 markers were found in 7/24 sporadic cases and in 3/3 MEN-1 cases The deletions were mapped to a small region within chromosome 11q13.

Cytometric DNA assessments were made by means of image cytometric and flow cytometric analyses. Twenty-one sporadic lesions were DNA euploid and three aneuploid, whereas the familial cases were diploid. Two of the aneuploid cases had allele losses. Histopathologic features showed adenomas in 18 cases and hyperplastic glands in 9 cases, among these latter were 2/3 MEN-1 patients. No correlation was found between the morphology of the tumours and the allele losses.

By studying sporadic and hereditary lesions of hyperparathyroidism the disease gene has been localized to a small region within chromosome 11q13. The findings are consistent with other published studies indicating unmasking of a recessive cancer gene as a possible cause of the development of sporadic as well as hereditary parathyroid lesions.

Relationship between DNA analysis and parathyroid pathology

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The aetiology of hyperparathyroidism is unknown and histological classification of the disease is difficult with poor diagnostic predictability.

The nuclear DNA content of 85 parathyroid glands (4 carcinomas, 39 adenomas, 21 secondary parathyroid hyperplasias and 21 normal parathyroid glands) was determined by flow cytometric analysis. All normal glands, 85 per cent of the adenomas and 83·3 per cent of the secondary hyperplastic glands, had DNA indices within values of 0·85–1·1. Paraffin-embedded fixed glands showed less DNA staining than fresh or normal glands. All carcinomas showed DNA indices outside the normal DNA index range. When the percentage of nuclei within the G0/G1 phase of the cell cycle was compared in the study groups, highly significant results were found. All patients with secondary hyperplasia showed a distribution similar to that in the normal glands studied. Only 48 per cent of primary adenomas showed >80 per cent of cells within the G0/G1 region A clear subgroup of adenomas was defined with more rapidly cycling tetraploid cells and showing 'classical' adenoma pathology. This group showed negative correlation with gland weight, plasma calcium and ionized calcium These findings possibly demonstrate a different aetiology of the disease process between secondary hyperplasia and parathyroid adenoma Such abnormal glands form a group worthy of long-term follow-up.

Use of whole-molecule parathyroid hormone measurement during parathyroidectomy

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The recent introduction of whole-molecule-specific parathyroid hormone (PTH) assays has facilitated the measurement of PTH in clinical practice. Modification of the assay conditions allow results to be available within one hour of sampling. PTH itself disappears rapidly from the peripheral blood following successful parathyroidectomy The rapid PTH assay and appropriate timing of blood sampling permit PTH levels to be reported rapidly following parathyroidectomy.

We have performed intra-operative monitoring of PTH levels during parathyroidectomy in a total of 45 patients. PTH levels declined to <20 per cent of the initial value within 20 min of parathyroidectomy in 39 patients. All of these patients underwent successful surgery, defined by a combination of histological frozen section and serial serum calcium measurements. In a further three patients with chronic renal failure, PTH declined to <40 per cent of initial value In four patients, PTH failed to fall below 60 per cent of the initial value. Two of these were re-explored during the same operating session and further parathyroid tissue removed from one patient. The remaining three patients had persistently elevated serum PTH and calcium levels Intra-operative PTH monitoring is now provided as part of the routine laboratory service to the surgeon and is of assistance in the early detection of residual functioning parathyroid tissue during parathyroid surgery

Technetium-99m sestamibi for parathyroid imaging

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A preliminary report has suggested that the isonitrile technetium-99m sestamibi could be used as an alternative to thallium-201 in pre-operative localization of parathyroid glands. To compare these agents, we have investigated 42 patients with suspected hyperparathyroidism and to date 18 have undergone surgical exploration

The thyroid was localized using ^{123}I Dynamic acquisition was obtained for 20 min following iv administration of ^{201}Tl and for a further 20 min for ^{99m}Tc sestamibi After allowing for scatter, conventional subtraction procedures were performed Of the 18 patients who had surgery, 11 had adenomas (10 positive with ^{99m}Tc sestamibi, 8 positive with ^{201}Tl, 1 missed on both scans), 5 patients had hyperplastic glands (12 positive glands identified with sestamibi, 10 with ^{201}Tl) and 2 patients with metastatic parathyroid carcinoma had abnormal uptake with both agents.

Six patients (two adenomas, two hyperplasias, two carcinomas) were given tracer doses of both ^{201}Tl and ^{99m}Tc sestamibi shortly before the removal of the abnormal parathyroid tissue, and uptake in this was measured These biopsy data showed higher uptake of sestamibi than thallous chloride in abnormal parathyroid tissue Thus ^{99m}Tc sestamibi appears superior to ^{201}Tl for localizing abnormal parathyroid glands and gives a lower radiation dose However, it is more expensive than thallium and this may limit its routine adoption for parathyroid imaging.

Screening for multiple endocrine neoplasia type

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Multiple endocrine neoplasia type 1 (MEN 1) is a familial condition inherited in autosomal dominant manner, characterized by primary hyperparathyroidism (multiple gland hyperplasia 95 per cent), pancreatic islet cell tumours (65 per cent) and pituitary adenomata (prolactinoma 5 per cent) Screening of family members will permit the identification of affected relatives and allow early treatment of the condition before the onset of complications.

We have employed a new sensitive immunochemiluminometric assay (ICMA) specific for intact parathormone (PTH) together with measurement of serum calcium and prolactin to screen 97 relatives of patients with proven MEN 1 (10 families) and 25 relatives of patients with non-MEN 1 familial hyperparathyroidism or multiple parathyroid gland hyperplasia. Five MEN 1 relatives with abnormal biochemical results had significant clinical symptoms (renal calculi 2, duodenal ulcer 2, secondary amenorrhoea 1) Fifteen MEN 1 relatives had clinical or biochemical evidence of MEN 1 syndrome

	No	Raised PTH	Raised Ca	Raised prolactin
Non MEN 1 familial HPT	25	2	1	0
MEN 1 relatives				
First degree	67	19	12	3
Second degree	30	3	2	0
Total	122	24	15	3

It is concluded that screening of MEN 1 relatives is worthwhile and the intact parathormone assay (ICMA) increases diagnostic sensitivity

Correspondence

Intragastric balloons for morbid obesity

Sir
Mathus–Vliegen and Tytgat (*Br J Surg* 1980, 77. 76–9) state that ultimately surgery may be required for the treatment of morbid obesity but that it may not be feasible because of the high risks. It is time that surgery in this condition was put into perspective. There is no non-surgical treatment which will produce effective and sustained weight loss in this intractable disease. The risks of gastroplasty in experienced hands are no greater than that of cholecystectomy with Mason *et al* reporting a mortality rate of 0·3%[1]. With modern surgical and anaesthetic techniques this surgery can be done safely even in older patients (55–60 years)

A double blind controlled study of sham and balloon treatment done by Baird's group showed that the balloon was effective in producing weight loss over 3 months of 7·3 kg (±6·1) compared with 3·3 kg (±3 9) in the sham group[2] However, there is no data showing that this is an effective long-term treatment and in fact most patients regain their weight when the balloons are removed Weight loss of this degree is unsatisfactory in the morbidly obese We do not agree that the intragastric balloon will facilitate weight loss before planned obesity surgery and a collaborative study between ourselves and Baird showed that this was an effective method of weight reduction in patients on the waiting list for gastroplasty[3]

The literature now demonstrates that the intragastric balloon is not effective in the morbidly obese[4,5]. The area where further work needs to be done is in those patients who are overweight to a lesser degree (130–160 per cent of ideal body weight) where surgery is not indicated as lesser degrees of weight loss are required

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Technique for temporary purse-string suture

Sir
The article by Holscher and Siewert on the purse-string staple device (*Br J Surg* 1990, 77 526) illustrates one of the products of recent technological advances in stapling instruments that could be of considerable value to the gastrointestinal surgeon Undoubtedly, the instrument described has shown its worth in those cases of difficult access high in the chest and low in the pelvis, but I would like to express a few words of caution on two points

First, when the jaws of the instrument are placed across the tissue in which the purse-string is to be inserted it is important to ensure that the tissue abuts against that end of the jaws containing the loop of the suture material If this is not done, once the gun has been 'fired' there will be several loose staples and a redundant loop of suture material If this occurs it is relatively easy for the loop to come away from the stapled tissue, with the result that not all the cut end of the oesophagus or colon will be drawn onto the shaft of the circular staple gun

The second point concerns the method of cutting the tissue once the instrument has been 'fired' *Figure 1* shows the tissue being cut flush on the instrument with a scalpel. If the tissue is divided in this manner, the distance between the edge of the tissue and the row of staples which hold the purse string is minimal and the staples can dislodge easily. It is safer to divide the tissue with a pair of scissors and leave several millimetres between the free end and the row of staples

As the authors state, the present instrument is rather bulky and a much smaller one will be needed for the high intrathoracic oesophageal anastomosis

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Urine acid output after a test meal

Sir
We were impressed by Johnson and Rai's paper (*Br J Surg* 1990; 77 417–20) describing differences in urinary acid secretion between normal subjects and postvagotomy patients. Their method would appear to offer advantages in terms of simplicity and patient acceptability over current tests of the completeness of vagotomy We are, however, unable to agree with their statement that 'urine acid output after a test meal is always in a negative direction in normal subjects' Several months ago we conducted a similar experiment over 3 days on five healthy volunteers aged 18–45 years, each of whom consumed a standard test meal consisting of 100 g of kipper, 60 g of bread, 30 g of butter, 30 g of strawberry jam and 250 ml of coffee. The subjects were required to fast from midnight and to void a baseline urine sample before consuming the meal All the volunteers were non-smokers

The methodology for estimating urinary acid output was identical to that employed by Johnson and Rai. The median urinary acid output 2 h following the test meal was zero mmol/h (range −2 15–1 4 mmol/h) Variations in acid output from positive to negative were observed not only between subjects but also in the same subject on successive days We have repeated the experiment using the test meal described by Johnson and Rai and have found a similar variation from −0 9–1 3 mmol/h. It would appear from these data that urinary acid output is not invariably reduced in a normal postprandial subject

Urine acid output may prove to be a useful test of the completeness of vagotomy, but we would suggest that further verification of the normal range is required

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Author's reply

Sir
Novell and Dawson are correct to state that further validation of the normal ranges is required before postprandial urine acid outputs can be used in the clinical setting. We have continued our work with this test and we have also found that the response in normal subjects is wider than the range we originally reported. These studies are currently being prepared for publication

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Metabolic effects of cancer

Sir

I read with great interest the article by Douglas and Shaw (*Br J Surg* 1990; **77**: 246–54). We have for some years been studying this phenomenon mainly in relation to patients with gastrointestinal malignancy. We feel, however, that it would be wrong to attribute the glucose intolerance in the setting of malignancy, mainly to such intercurrent factors as sepsis, weight loss and bed rest. Whilst these factors can be of importance in the grossly cachectic cancer patient, abnormalities can be demonstrated before the onset of significant cachexia[1,2]. One of the difficulties in the interpretation of previous studies has been the tendency to mix all cancer patients together as a homogeneous group, whereas varying metabolic abnormalities can be seen in different histological types of cancer[2,3]. The same problem is also inherent to many previous and widely quoted studies of malnutrition, where patients with sepsis and malignancy had been included in the study group.

There is certainly clear evidence that in some distinct cancer groups glucose intolerance can be demonstrated before the onset of cachexia and that this appears to be related to peripheral insulin resistance[1,2]. Our previous and present studies would suggest that this represents a postreceptor defect in insulin action situated at a skeletal muscle level. Whether this represents a direct cancer effect or is the result of a host lymphocyte/tumour inter-reaction remains unclear, but there do appear to be qualitative differences in the insulin resistance of cancer and sepsis[1,2]. Indeed, the stress response of controls and patients with gastrointestinal malignancy are different[4].

We would agree that the metabolic abnormality of the grossly cachectic cancer patient is a more complex and multifactorial event than has previously been assumed, but there are cancer-induced abnormalities before this which we must understand, as they could have potential effects on our therapeutic endeavours[4].

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Extrapleural intercostal analgesia after thoracotomy

Sir

We read with interest the article on the extrapleural infusion of bupivacaine by Sabanathan *et al.* (*Br J Surg* 1990; **77**: 221–5). The authors emphasize the efficacy and the restoration of pulmonary function provided by this method. The absence of significant side-effects suggests that this technique could be a panacea after thoracotomy. However, a serious ventilatory impairment may occur after paravertebral infusion of local anaesthetics as we encountered in the following case.

A 64-year-old man (height 1·69 m, weight 92 kg) had undergone an upper lobectomy for cancer. He was a heavy smoker and investigation showed a mild obstructive pulmonary disease. Surgery was performed through a right posterolateral thoracotomy. Anaesthesia was induced and maintained with pentothal, vercuronium, fentanyl, halothane and 100 per cent oxygen. A paravertebral catheter was placed as described by Sabanthan *et al.* before closure of the chest. On arrival in the recovery room, a bolus of 20 ml bupivacaine 0·5 per cent with epinephrine was administered in a semi-sitting position. Half an hour later the patient still had pain and so intravenous paracetamol (1 g) and intramuscular morphone (10 mg) were injected. One hour later, no thoracic analgesia was found except at the level of the 10–11th thoracic dermatomes. At this time, an infusion of 6 ml/h of bupivacaine 0·25 per cent with epinephrine was begun. Then the ventilatory patterns worsened progessively, and 6 h later the patient was breathless and restless with a feeling of imminent death; clinical examination found an immobile right hemithorax with an extensive unilateral anesthesia to pinprick from T3 to T12; arterial oxygen saturation, measured by a pulse oxymeter, dropped from 94 to 82 per cent and no significant haemodynamic change was noted. The local anaesthetic infusion was stopped and inspired oxygen fraction was increased to one, 1 h later the patient began to recover without needing a ventilatory support.

Three comments may ensue from that case. 1) the initial bolus was not followed by a consistent analgesia; this might result from an interpleural diffusion through the leaky pleural wound, 2) the continuous infusions of 6 ml/h bupivacaine 0·25 per cent (less than the one proposed by Sabanathan *et al.*) effectively produced an extensive thoracic sensory block; and 3) a motor blockade of intercostal muscles was observed despite the use of low concentration bupicavaine.

In chronic obstructive pulmonary disease patients, intercostal and accessory muscles are involved in normal breathing patterns because functional residual capacity is increased. Conversely, in obese patients the functional residual capacity is reduced as the weight of the torso and abdomen make diaphragmatic excursions more difficult and more position dependent. After pulmonary resection in normal subjects, diaphragmatic function is preserved but intercostal/accessory muscle recruitment is increased at rest[1]. We think that normal activity of these muscles may be mandatory in chronic obstructive pulmonary disease or obese patients after thoracotomy. Consequently, a reduction of the bupivacaine concentration from 0·5 to 0·125 per cent, in order to limit the risk of a motor blockade, and close monitoring are needed for safer use of extrapleural intercostal analgesia in such patients.

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1. Maeda H, Nakahara K, Ohno K *et al.* Diaphragm function after pulmonary resection – relationship to postoperative respiratory failure. *Am Rev Respir Dis* 1988; **137**: 678–81.

Asymmetrical nature of the muscular anatomy of the infantile pylorus

Sir

I congratulate Messrs Cass and Bond (*Br J Surg* 1990; **77**: 919–21) on their elegant anatomical studies on the infantile pylorus. Neither district general nor reference hospitals can afford to be complacent when internationally famous hospitals have to report mucosal perforation in 8·5 per cent of pyloromyotomies[1].

Cass and Bond mention in passing how they test if the pyloromyotomy is complete at the duodenal end. 'If the muscle in either side of the incision moves independently then the incision is sufficient'. This test seems to have been ignored in British postgraduate teaching (until now I thought that I had invented it).

Independent movement between the upper and lower edges of the cut muscle is sought as the distal last few fibres are ruptured with an Ash dissector[2]. The movement is small, akin to a gunsmith testing for a 'tight action', but the end-point for independent movement is sharp and the surgeon in training can be confident that division is complete and that he must stop.

The teaching[1] that mucosal perforation during pyloromyotomy, if recognized, is of little consequence may be true, but undervalues surgical craftmanship. One mucosal perforation in a surgical lifetime (personal communication) is more than one should allow oneself.

If the above test for completion of muscle division is carefully carried out, perforation of the duodenum mucosa will not occur. 'Repeat' pyloromyotomy also disappears.

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Thromboprophylaxis – combination of graduated compression stockings and pharmacological substances

Sir

The review on graduated compression stockings in the prevention of postoperative deep vein thrombosis by Jeffery and Nicolaides (*Br J Surg* 1990; 77: 380–3) is an up-to-date analysis and therefore welcome. The number of studies is large enough (there are 31 studies published against the 16 used by the authors) to conclude that graduated compression prevents deep vein thrombosis in many postoperative situations and it is easy to agree on many points in the article. However, the recommendations are not totally based on data presented in the paper The authors conclude that graduated compression stockings should always be used. This is a very firm recommendation where a calculation of cost-effectiveness would be most welcome. In moderate and high risk groups they 'recommend the third option, using either low dose heparin, low molecular weight heparin, or intermittent compression as an additional agent'. As an overall conclusion this is probably justified but perhaps not that clearcut There is a total of 15 studies where graduated compression, with dextran (5), low dose heparin (7) and intermitent compression (3) is compared with some sort of control, that is not the combination. Although most of the studies are small and therefore do not give significant results, only in two of the studies are the frequencies of deep vein thrombosis higher than in the combination group. Moreover, we have two specific comments on the conclusions. First, our study on dextran and compression stockings is listed in *Table 2* in their paper and it clearly shows this to be a very effective combination without side effects in elective abdominal surgery[1]. This finding has further been supported in patients undergoing elective hip surgery, although not to the same dramatic extent[2]. The group with compression stockings also had a significantly smaller intraoperative blood loss. Thus, it seems fair to suggest that the combination of graded stockings and dextran is also effective and, therefore, could be included in the concluding recommendation. Second, the recommendation to combine compression stockings with low molecular weight heparin is not supported by controlled studies nor by data in the review. A potential effect will be difficult to show as the frequency of deep vein thrombosis is very low with low molecular weight heparin prophylaxis, at least in general surgery As a final point it seems fair to comment that there are no studies (single ones or meta-analyses) where a reduction in fatal pulmonary embolism has been documented by using graduated compression stockings

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Percutaneous endoscopic gastrostomy

Sir

Moran and colleagues are to be congratulated on their review (*Br J Surg* 1990, 77· 858–62) highlighting the technique of percutaneous endoscopic gastrostomy (PEG) Like them we believe this technique has the potential for much wider use in clinical practice than is currently the case We disagree that the procedure is best performed by surgeons so they can deal with the complications (by implication the authors are therefore suggesting that all therapeutic endoscopic procedures should be done by surgeons), but would insist that it should be done under the supervision of an experienced therapeutic endoscopist

The authors are correct in stating that this technique is most commonly indicated as a route of access for patients requiring enteral nutrition support, but we feel they could be more precise in defining when a PEG should be placed. Our own practice is to consider a PEG for any patient in whom nutritional support is likely to be required for more than 1 month Thus, neurological patients (acute onset or chronic progressive) comprise the largest group for whom we place PEGs. For those patients with chronic neurological causes of impaired deglutition (e g. motor neurone disease, multiple sclerosis), we now liaise with our speech therapists who can objectively measure progressive deterioration using cinevideoradiography. If it is observed that the patient is aspirating whilst swallowing we discuss with the patient and their family the timing of placement of PEGs, in order to obviate the need for any prolonged period of nasoenteral intubation. We would disagree that a 'confusional state' should be listed with the conditions that may be appropriate for PEG insertion – it is more correctly grouped as a relative contraindication because of the risk of early tube dislodgement[1]

The authors emphasize the need to have suction available to clear the pharynx of secretions which may be aspirated, but the risk of aspiration may also be decreased by tilting the patient's head down 5–10°. In their description of the 'pull method' they describe the use of the suture 'which may break or come undone'. It is true to say that the problem has been 'practically eliminated' but it may be avoided completely by using kits that use wire loops that will not break and can be grabbed by specially designed endoscopic forceps[2]. It is not true that all 'pull PEGs' require a further endoscopy for removal at the end of treatment – the tube in current use in our unit (Bower PEG®, Corpak, E. Merck, Four Marks, UK) can be removed with firm traction, after deflation of a preformed polyurethane foam filled balloon

The major complications of PEG occur more commonly than the authors state, and gastrocolic fistulae appear to be predominantly a paediatric problem[3], although we have been recently made aware of a case of gastrocolic fistula in an adult patient in the UK Necrotizing fasciitis occurs more frequently than suggested in the review, and is not necessarily prevented by ensuring an adequately large skin incision[1,4–7]. A high index of suspicion must be maintained in the presence of localized signs after PEG insertion for the development of this potentially fatal complication so that treatment can commence at the earliest opportunity It is important to note that pneumoperitoneum can also develop after PEG (in up to 38 per cent of cases) and may be considered a benign finding in the absence of signs or symptoms of peritoneal inflammation It may persist in some cases for weeks[8]

Finally, the authors are incorrect to state that no randomized, controlled trial of operative *versus* percutaneous gastrostomy has been done The final results of a study first reported by Stiegmann *et al.*[9], have recently been published and suggest that the two methods are comparable in terms of morbidity and mortality when both are done with local anaesthesia, but PEG incurs less financial cost[10], an advantage that is now of particular relevance to those working in the National Health Service

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Book reviews

Screening for Colorectal Cancer

Proceedings of an international meeting J. D Hardcastle, ed 143 × 203 mm. Pp. 110 Not illustrated. 1990. Bad Homburg, FRG. Normed Verlag $16 00 softback.

Colorectal cancer is a major cause of death from malignant disease As the adenoma–carcinoma sequence is thought to take many years there is, in theory at least, potential value in screening patients for early stage disease The subject of screening for colorectal cancer was addressed at an international meeting in May 1989 organized by the UK Coordinating Committee on Cancer Research both within high risk groups and in the average risk population The proceedings of the meeting are reported in this booklet edited by Professor J D. Hardcastle

Population screening studies using faecal occult blood testing are reported from Europe and USA with in general a response by 50 per cent of the population This leads to the detection of adenomas and early carcinomas as well as more advanced tumours but the effects on long-term survival awaits the results of ongoing trials of which the Nottingham study seems most likely to give meaningful data. Chapters on colonoscopic follow-up of high risk patients with adenomas and carcinomas indicate that further tumours can be detected by this means. The returns, however, are relatively small with some risk of perforation and haemorrhage.

A chapter on family cancer screening by Dr Murdy illustrates the value of family studies and a clear review of the role of screening for long standing ulcerative colitis is presented by Professor Leonard Jones.

Whilst the precise value of screening for colorectal cancer is as yet uncertain, the techniques at present available are accurately presented in this booklet

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Last's Anatomy: Regional and Applied. 8th edn.

R M H McMinn, ed. 182 × 243 mm Pp. 650 Illustrated 1990. Singapore Churchill Livingstone £27 50 softback

Last's text, whch has been so popular since the first edition in 1954, has been the standard anatomical text for most young surgeons taking their Primary FRCS examinations in Anatomy It is not difficult to see why the book has been supremely successful It combines a vibrant readable text with good clear diagrams and clinical relevance which is given poignance by just the right amount and flavour of anecdotal material It is such a personal account of the subject that it is difficult to see how anyone might revise the text for a new edition and retain Last's original touch of genious Professor McMinn has achieved all this in the revised eighth edition The book has 100 more pages than before and these are largely taken up with new diagrams by Philip M. Bull, Chief Medical Artist at Addenbrooke's Hospital, University of Cambridge, computed tomographic scans and additional clinical text The new clinical items are timely in view of the changing emphasis of the new Fellowship examinations. Readers familiar with the old text will be pleased to discover that the nervus intermedius is now definitely part of the VIIth cranial nerve complex, that the inferior rectal vessels and nerves now traverse the ischiorectal fossa and that the lunate fascia receives no mention. No doubt it will also be reassuring to find that the fruit bat still makes its point about the functional significance of the popliteus muscle in weight bearing animals R M H McMinn's new edition of *Last's Anatomy* perfectly updates this first class book to enable it to maintain pride of place in current anatomical texts and be essential reading for all aspiring and practising surgeons

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Pancreas Transplantation: Experimental and Clinical Studies

J-P. Squifflet 175 × 245 mm Pp 188 Illustrated 1990 Basel, Switzerland Karger £61 30 hardback

This slim publication is no more than it pretends to be a somewhat expanded publication of the author's research thesis It is clear that the experimental work for the thesis was performed some 8 years ago and more recent clinical material has been added subsequently, presenting the extensive experience of the Minneapolis group, to which Dr Squifflet was an active contributor, and the limited experience of Dr Squifflet at Louvain, Belgium The author presents a good summary of the development of vascularized pancreatic transplantation, and makes some comments on pancreatic islet transplantation, although this section is covered less well and is badly out of date, with no reference to the considerable advances in this field over the past 5 years. The sections on selection, operative technique and management of patients after vascularized pancreatic transplantation are good, well referenced, and would be of interest to clinicians performing vascularized pancreatic transplants The section on results is, in the main, derived from the Pancreas Transplant Registry data, which have been extensively reported elsewhere This section is of lesser interest, particularly as it is based on data taken up to April 1987, and is thus severely out of date In conclusion, this volume is variable in quality, but does contain material of interest to the clinician directly involved with vascularized pancreatic transplantation.

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Clinical Gastroenterology International Practice and Research. Liver and Pancreas Transplantation

W Creutzfeldt, R Pichlmayr, eds. 155 × 232 mm Pp. 890 Illustrated 1989. London. Baillière Tindall £22 50 hardback

This volume attempts in only 143 pages to review the growing fields of liver and pancreas transplantation. It achieves this apparently impossible task remarkably well gathering together expert authors in these fields from England, Germany and Sweden Each of the 11 sections is fully referenced drawing on published works from leading groups throughout the world and presenting a balanced and up-to-date review of the literature.

All aspects of liver transplantation are covered in individual chapters ranging from organ harvesting, patient selection and the optimal timing of transplantation in chronic liver disease to recent technical advances, immunosuppression and specialized indications such as metabolic disorders and liver tumours Pancreas grafting is similarly well covered including sections on both whole organ and islet grafting and discusses not only the surgical techniques and results but also the more difficult field of the relative merits of intensive insulin therapy *versus* transplantation in preventing secondary complications Excellent line drawings are used to illustrate the sections dealing with the technical aspects of liver and pancreas grafting although similar drawings would have been useful in the section on organ procurement to supplement the detailed operative descriptions given in the text

In summary this is an excellent review of two exciting areas in transplantation covering the present 'state of the art' in both fields The two editors are to be complimented both on their choice of authors and the way in which they have avoided overlap in the subject matter of the various sections The book will be of interest to transplant surgeons as an update in recent progress but is also sufficiently comprehensive and clearly written to be recommended for any surgeon with an interest in gastroenterology seeking an introduction to these topics

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Therapy of Advanced Melanoma. Vol. 10

P. Rümke, ed 170 × 245 mm Pp. 230 + viii Illustrated. 1990 Basel, Switzerland Karger. £82.50 hardback

This is a useful summary of current therapy available for advanced melanoma, written by authorities in the various treatment areas. It deals in detail with metastatic disease, much less so with adjuvant therapy of poor risk cases, but this is not surprising in view of the general lack of efficacy of these agents. Surgery, radiotherapy and chemotherapy are well covered in the first half, with a good account of the value of isolated regional perfusion. The second half deals with the area of biological response modifiers, potentially exciting but yet to be translated to usefulness in routine clinical practice. The references are up-to-date with a few from 1989.

Anyone looking for a quick summary of this field would find the book useful, and it would be a valuable addition to libraries of any hospital with an oncological interest. Those working in the field will probably be well aware of the material in this book, and will be looking to the latest results with biological response modifiers

The index unfortunately is hopelessly inadequate, and out of keeping with the production quality of the rest of the book

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Nails: Therapy, Diagnosis, Surgery

Scher and Daniel 190 × 264 mm. Pp. 302. Illustrated. 1990. London W. B. Saunders Co. £78 50 hardback.

This is a compact but comprehensive multi-author text dealing with the normal and abnormal nail and nailbed The book provides up-to-date information concerning nails and is directed widely in an attempt to interest general physicians, dermatologists, surgeons, pathologists, basic scientists, cosmeticians, and the pharmaceutical industry. The first five chapters cover the normal nail and make a useful reference section to help understand the pathologies which may affect the nail and nailbed.

The remainder of the book is of limited interest to the general surgeon, but does contain two concluding chapters on nail surgery, one on basic surgery and one on advanced surgery The former chapter would be of interest to the junior general surgeon, while the latter chapter might be of interest to accident and emergency specialists or orthopaedic surgeons with an interest in hand surgery

In summary, this publication will be a useful reference text, but not a book that will be commonly found in a surgeon's personal library.

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The Cause and Management of Aneurysms

R. M. Greenhalgh, J. A. Mannick, eds. 170 × 250 mm Pp. 475 Illustrated. 1990. London W B. Saunders Co. £55.00 hardback.

It seems that there is an 'epidemic' of aortic aneurysms in Western society and this book, which contains 44 separate pieces better described as 'monographs' than 'chapters', is timely. Many aspects of aneurysms are explored and, not surprisingly in view of the book's editorial provenance, it is aneurysm of the abdominal aorta that has pride of place. There are 76 contributing authors from across the world: 29 from the UK and Ireland, 22 from continental Europe, 21 from North America, and four from elsewhere. The list of contributors contains mostly well known vascular surgeons whose considerable experience lends great authority to the volume.

Well over half the book is devoted to the clinical management of aneurysms, including a specific section on inflammatory lesions. This text is written by acknowledged experts for practising surgeons A further section deals with practical aspects of presentation and investigation. Of the 475 pages, 76 are devoted to the mechanism of dilatation which is an area of 'expanding' interest in vascular surgical circles. The book is liberally and clearly illustrated with clinically-related material and, for the most part, the monographs are backed up by extensive and up-to-date references.

It is difficult to construct a well integrated volume when it is necessary to accommodate the idiosyncracies of so many individual authors. Nevertheless, this book has little in the way of overlap between monographs and the differences of opinion expressed by different authors shed a useful light on where the current controversies in aneurysm management lie. This is a book for experienced surgeons and those in training who intend to make vascular surgery a particular interest It is an excellent reference work for any vascular unit and comes highly recommended.

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Spot Diagnosis in General Surgery

H Ellis. 146 × 210 mm. Pp. 240. Illustrated. 1990 Hong Kong· Blackwell Scientific £9 95 paperback.

The place to learn to recognize common surgical conditions is in the out-patient department, and there is no substitute for this theatre of life, in which cases are taken 'straight from the street' and transformed into patients who have been accurately diagnosed and properly handled. In many teaching centres the time allocated for surgical instruction has been drastically cut, and in a few such centres 'common' surgical conditions are rather rare. Professor Ellis has produced an excellent book to supplement, or even partially replace, didactic instruction of clinical students in the basics of out-patient recognition of surgical cases. The photographs are superb, and the accompanying questions are cunningly devised to test large parts of the essential information required about each condition For those of us who know Professor Ellis's stature as a teacher this is no surprise and the text reflects his outstanding qualities of clarity, incisiveness and vigour. I recommend familiarity with this book to every undergraduate who is approaching his Finals, which will go far to ensure success in the 'short cases' section of his clinical examination.

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Surgical Endocrinology: Clinical Syndromes. 2nd edn.

S. R. Friesen, N W Thompson, eds 190 × 260 mm. Pp. 454. Illustrated. 1990. Philadelphia, USA J. B. Lippincott Co. $79 50 hardback

A signal feature of the past decade has been the foundation of national surgical endocrine associations not only in the UK and USA but also in many European countries They flourish and prosper showing that surgical endocrinology, both the science and practice, are vibrant and active. This dynamism is reflected in this book – *Surgical Endocrinology Clinical Syndromes* Thirty-nine authors from five countries have contributed to this second edition which is divided into two sections. The first deals with recent advances in diagnosis and management and the second with clinical syndromes. Each chapter is concisely written with a logical sequence characterized by excellent illustrations and a comprehensive bibliography A particular and welcome feature is that the editors are not passive collators but make an individual comment at the end of each chapter; such active participation and distilled experience is invaluable

This is an excellent book, easy to read, up-to-date and avoiding a dogmatic format but with a formative style There is something here for any surgeon A definitive guide for the fellowship candidate and a valued reference book for the established surgeon. It certainly deserves a place in every postgraduate centre library and on the bookshelf of the surgeon with an endocrine interest

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Notices and announcements

13–16 November 1990
2nd International Interdisciplinary Symposium
Vienna, Austria
Information Peritoneum and Peritoneal Access (PAX), F Schulz, c/o Vienna Academy of Postgraduate Medical Education and Research, Alser Strasse 4, A-1090 Vienna, Austria

13–16 November 1990
Peritoneum and Peritoneal Access
Vienna, Austria
Information PAX Secretariat, c/o Vienna Medical Academy, Alser Strasse 4, A-1090 Vienna, Austria

15–17 November 1990
Second International Congress on Access Surgery
The Netherlands
Information: Conference Agency Limburg, Mrs M. Frank-Roovers, University Hospital Maastricht, PO Box 1918, 6201 BX Maastricht, The Netherlands

15–17 November 1990
10th Annual WBAMC Trauma Symposium
El Paso, Texas, USA
Information. Mrs Marty May, Secretary to Maj Stephen D. Carey, Trauma Service/SICU, William Beaumont Army Medical Center, El Paso, Texas 79920-5001, USA

24–27 November 1990
Recent Advances in Anaesthesis, Pain, Intensive Care and Emergency
Italy
Information: Trieste Traduzioni Congressi, 34125 Trieste, Italy

26–29 November 1990
6th International Symposium on Cardiopulmonary Urgencies and Emergencies
Rotterdam
Information Omar Prakash, Thorax Centre, Erasmus University, Postbus 1738, 3000 DR Rotterdam, The Netherlands

2–5 December 1990
The 7th Asia—Oceania Congress of Otorhinolaryngological Societies
Hong Kong
Information Congress Secretariat, 1/F 57 Wyndham Street, Central, Hong Kong

6–8 December 1990
1st International Symposium on Benign Breast Disease and Chemoprevention of Breast Cancer
Genoa, Italy
Information Oncologia Clinica, Istituto Nazionale per la Ricerca sul Cancro, Viale Benedetto XV, 10, 16132 Genova, Italy

11–13 December 1990
5th International Workshop on Therapeutic Endoscopy
Hong Kong
Information: Joseph W. C Leung, Senior Lecturer in Medicine, Prince of Wales Hospital, Shatin, Hong Kong

18–20 January 1991
The 27th Head and Neck Course
Liverpool, UK
Information: Professor P. M. Stell, Department of Otorhinolaryngology, University of Liverpool, Royal Liverpool Hospital, PO Box 147, Liverpool L69 3BX

19–20 January 1991
Hong Kong Surgical Forum
Hong Kong
Information Forum Secretary, Department of Surgery, University of Hong Kong, Queen Mary Hospital, Hong Kong

27 January–1 February 1991
Second European Winter Oncology Conference
Meribel, France
Information IMEDEX B,V, PO Box 3283, 5203 DG 's-Hertogenbosch, The Netherlands

1 March 1991
Aneurysmal Surgery
Bristol, UK
Information Mr M. Horrocks, Department of Surgery, Bristol Royal Infirmary, Marlborough Street, Bristol BS2 8HW, UK

17–19 April 1991
International Conference on Railway Suicide
London, UK
Information Professor R. Farmer, Charing Cross and Westminster Medical School, 17 Horseferry Road, London SW1P 2AR, UK

18–21 April 1991
SAGES 1991 Scientific Session
California, USA
Information Program Committee, SAGES, Suite 409, 1271 Stoner Avenue, Los Angeles, CA 90025, USA

22–25 April 1991
4th International Symposium on Cardiovascular Pharmacotherapy
Geneva, Switzerland
Information ISCP'91, c/o AKM Congress Service, PO Box CH-4005, Basel, Switzerland

4–5 May 1991
5th International Meeting on Venous Disease
Sydney, Australia
Information Dr M Malouf, 32 Grose Street, North Parramatta, Sydney 2151, Australia

4–5 May 1991
5th International Meeting of the Australian and New Zealand Society of Phlebology
Sydney, Australia
Information: Dr G. Mark Malouf, Secretary, ANZ Society of Phlebology, PO Box 2166, North Parramatta 2151, Sydney, Australia

8–11 May 1991
XXVIth Congress of the European Society for Surgical Research and the VIIIth Tripartate Meeting of The Surgical Research Society and The Society of University Surgeons
Salzburg, Austria
Information ESSR Congress Office, 1st Surgical Department, Landeskrankenanstalten, Müllner Hauptstrasse 48, A-5020 Salzburg, Austria

15–18 May 1991
Annual Meeting of the American Association for Cancer Research
Houston, Texas, USA
Information: American Association for Cancer Research, Public Ledger Building, Suite 816, Sixth and Chestnut Streets, Philadelphia, PA 19106, USA

30 May–1 June 1991
4th International Symposium on the Biology, Immunology and Surgery of the Greater Omentum
The Netherlands
Information: Secretariat, 4th International Omentum Symposium, Mrs W J. Buys–Utrecht Cancer Research Centre, Servaasbolwerk 14, 3512 NK Utrecht, The Netherlands

2–14 June 1991
Methods of Immunologic Research and Diagnosis
Buffalo, New York, USA
Information James F. Mohn, Director, The Ernest Witebsky Center for Immunology, 272 Sherman Hall, Buffalo, New York 14214, USA

6–8 June 1991
5th European Congress of the Society for Surgery of the Shoulder and the Elbow
Wurzburg, FRG
Information: Prof. Dr med. J. Eulert, Orthpadische Universitatsklinik, Konig-Ludwig-Haus, Brettreichstr. 11, 8700 Wursburg, FRG

25–31 August 1991
International Surgical Week
Stockholm, Sweden
Information: Scientific Secretariat, 155, Hauptstrasse 63, PO Box 411, CH-4153, Reinach BL1, Switzerland

1–6 September 1991
6th World Congress in Ultrasound
Copenhagen, Denmark
Information: Spadville Congress Service, Sommervaj 3, DK-3100 Hornbaek, Denmark

SURGERY

CONTENTS, OCTOBER 1990
Volume 108 Number 4

Official Publication
SOCIETY OF UNIVERSITY SURGEONS, CENTRAL SURGICAL ASSOCIATION,
and AMERICAN ASSOCIATION OF ENDOCRINE SURGEONS

CENTRAL SURGICAL ASSOCIATION

Page 595 **Presidential address: The challenge of a new decade—A surgeon's perspective of the 1990s**
Jay L. Grosfeld, MD

601 **Lipid results of partial ileal bypass in patients with heterozygous, type II-A hyperlipoproteinemia**
Christian T. Campos, MD, John P. Matts, PhD, Laurie L. Fitch, MPH, Jane C. Speech, MS, John M. Long, EdD, Henry Buchwald, MD, PhD, *and* the Program on the Surgical Control of the Hyperlipidemias

612 **Prospective evaluation of clinical and pathologic detection of axillary metastases in patients with carcinoma of the breast**
Aaron H. Chevinsky, MD, John Ferrara, MD, Arthur G. James, MD, John P. Minton, MD, Donn Young, PhD, *and* William B. Farrar, MD

619 **Short-term tamoxifen plus chemotherapy: Superior results in node-positive breast cancer**
J. P. Crowe, Jr., MD, N. H. Gordon, PhD, R. R. Shenk, MD, R. W. Soegiarso, MS, C. A. Hubay, MD, E. G. Mansour, MD, J. M. Shuck, MD, DSc, O. H. Pearson, MD, J. S. Marshall, MD, B. Arafah, MD, A. R. Antunez, MD, R. E. Hermann, MD, J. C. Jones, MD, W. J. Flynn, MD, D. Evans, MD, R. W. Sponzo, MD, C. Eckert, MD, J. Horton, MB, CHB, W. L. McGuire, MD, *and* Participating Investigators

629 **Ascending cholangitis: Surgery versus endoscopic or percutaneous drainage**
H. S. Himal, MD, FRCS(C), FACS, *and* T. Lindsay, MD, CM

635 **Are cystgastrostomy and cystjejunostomy equivalent operations for pancreatic pseudocysts?**
Kenneth A. Newell, MD, Terrence Liu, MD, Gerard V. Aranha, MD, *and* Richard A. Prinz, MD

641 **Pancreatogastrostomy: A safe drainage procedure after pancreatoduodenectomy**
Romano Delcore, MD, James H. Thomas, MD, George E. Pierce, MD, *and* Arlo S. Hermreck, MD

648 **Early results of combined electrohydraulic shock-wave lithotripsy and oral litholytic therapy of gallbladder stones at the University of Iowa**
James W. Maher, MD, Robert W. Summers, MD, Thomas R. Dean, PA-C, J. Swift, BSN, D. Heitshusen, BSN, *and* G. Quinn, BSN

655 **Early tracheostomy for primary airway management in the surgical critical care setting**
Jorge L. Rodriguez, MD, Steven M. Steinberg, MD, Frederick A. Luchetti, MD, Kevin J Gibbons, MD, Paul A. Taheri, MD, *and* Lewis M. Flint, MD,

660 **Combined orthopedic and vascular injury in the lower extremities: Indications for amputation**
Mark D. Odland, MD, Victor L. Gisbert, MD, Ramon B. Gustilo, MD, Arthur L. Ney, MD, David P. Blake, MD, *and* Melvin P. Bubrick, MD

667 **Inadequate granulopoiesis after major torso trauma: A hematopoietic regulatory paradox**
Frederick A. Moore, MD, Verlyn M. Peterson, MD, Ernest E. Moore, MD, Christine Rundus, MT, *and* Renato Poggetti, MD

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676 **Subxiphoid pericardiotomy versus echocardiography: A prospective evaluation of the diagnosis of occult penetrating cardiac injury**
Ernesto Jimenez, MD, Marcel Martin, MD, Irvin Krukenkamp, MD, *and* John Barrett, MD

681 **The use of the Jarvik-7 total artificial heart and the Symbion ventricular assist device as a bridge to transplantation**
Roque Pifarre, MD, Henry J. Sullivan, MD, Alvaro Montoya, MD, Mamdouh Bakhos, MD, John Grieco, MD, Bryan K. Foy, MD, Bradford Blakeman, MD, Maria Rosa Costanzo-Nordin, MD, Rudolph Altergott, MD, *and* Vassyl Lonchyna, MD

686 **Heparin-induced thrombocytopenia in patients who undergo open heart surgery**
Joseph T. Walls, MD, Jack J. Curtis, MD, Donald Silver, MD, *and* Theresa M. Boley, RN

694 **The diagnosis and definition of hepatic malignancies by use of arterial enhanced computerized tomographic scanning**
Robert J. Goulet, Jr., MD, Inder Seekri, MD, Margaret Inman, MD, Kenyon K. Kopecky, MD, James A. Madura, MD, *and* Jay L. Grosfeld, MD

702 **Is DNA ploidy of prognostic significance in stage I cutaneous melanoma?**
P. Gattuso, MD, V. Reddy, MD, E. Solans, MD, S. Kathuria, MD, G. V. Aranha, MD, FRCS(C), H. K. Jacobs, PhD, *and* J. Walloch, MD

710 **Anomalies of intestinal rotation in childhood: Analysis of 447 cases**
Frederick J. Rescorla, MD, Frederick J Shedd, MD, Jay L. Grosfeld, MD, Dennis W Vane, MD, *and* Karen W. West, MD

717 **Long-term follow-up of the ileoanal anastomosis in children and young adults**
Robert L. Telander, MD, Michael Spencer, MD, Jean Perrault, MD, David Telander, BS, *and* Alan R. Zinsmeister, PhD

726 **Kidney transplantation in patients aged sixty years and older**
James A. Schulak, MD, James T. Mayes, MD, Kent H Johnston, MD, *and* Donald E. Hricik, MD

734 **Beneficial effects of fetal liver tissue on fetal pancreatic transplantation**
Lorraine Tafra, MD, Ronald Berezniak, PhD, *and* Donald C. Dafoe, MD

742 **Results of infrainguinal bypass for limb salvage in patients with end-stage renal disease**
Benjamin B Chang, MD, Philip S K. Paty, MD, Dhiraj M. Shah, MD, Jeffrey L. Kaufman, MD, *and* Robert P. Leather, MD

748 **Lower extremity percutaneous transluminal angioplasty: Multifactorial analysis of morbidity and mortality**
Jonathan E. Hasson, MD, Charles W. Acher, MD, Myron Wojtowycz, MD, John McDermott, MD, Andrew Crummy, MD, *and* William D. Turnipseed, MD

755 **Naloxone and spinal fluid drainage as adjuncts in the surgical treatment of thoracoabdominal and thoracic aneurysms**
Charles W. Acher, MD, FACS, Martha M. Wynn, MD, *and* Judy Archibald, RN

763 **Decreased parietal cell acid secretion after vagotomy is not associated with altered gastric prostaglandin levels**
Michael J Zdon, MD, Barry A Levine, MD, *and* Michael A. Quigley, BS

769 **Circadian esophageal motor function in patients with gastroesophageal reflux disease**
Hubert J. Stein, MD, Ernst P. Eypasch, MD, Tom R. DeMeester, MD, Thomas C. Smyrk, MD, *and* Stephen E. A. Attwood, FRCSI

This is a partial listing of October 1990 SURGERY contents